Nguyen, Quang (AU1632)

To: Chan, Christina
Subject: RUSH sequence search request for 09/827854

I would like to request a RUSH sequence search for the above application because it is an amended case due this bi-week.

Please search:

(1) A nucleic acid sequence encoding the amino acid sequence of SEQ ID NOs: 14, 15, 16, 17, 18 and 19;

(2) A nucleic acid sequence encoding amino acid residues 1-277 of SEQ ID NO:15;

(3) A nucleic acid sequence encoding amino acid residues 1-203 of SEQ ID NO:15;

against commercial, issued U.S. patent and pending patent application databases.

I am in AU 1636, my mailbox is in CM1-11E12.

THANK YOU.

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT,PGPB,JPAB,EPAB,DWPI,TDBD; THES=ASSIGNEE; PLUR=YES; OP=AND		
L5	((EpoE3) or (EpoE adj 3)) and (hyperlipidemia or cholesterol)	7	L5
L4	L2 not L3	50	L4
L3	L2 and (hyperlipidemia and cholesterol)	6	L3
L2	((apoliprotein adj E) or (apoE?)) same (truncated or fragment or deleted)	56	L2
L1	Zannis-Vassilis-I$.in.	3	L1

END OF SEARCH HISTORY

Status: Path 1 of [Dialog Information Services via Modem]

Status: Initializing TCP/IP using (UseTelnetProto 1 ServiceID pto-dialog)
Trying 31060000009999...Open

DIALOG INFORMATION SERVICES
PLEASE LOGON:
 ******** HHHHHHHH SSSSSSSS?
Status: Signing onto Dialog
 ****
ENTER PASSWORD:
 ******** HHHHHHHH SSSSSSSS? ********
Welcome to DIALOG
Status: Connected

Dialog level 02.18.00D

Last logoff: 23jul03 15:41:16
Logon file001 28jul03 13:41:27
*** ANNOUNCEMENT ***
***
--File 654 - US published applications from March 15, 2001 to the present are now online. Please see HELP NEWS 654 for details.

***
--File 581 - The 2003 annual reload of Population Demographics is complete. Please see Help News581 for details.

***
***
--File 990 - NewsRoom now contains February 2003 to current records. File 992 - NewsRoom 2003 archive has been newly created and contains records from January 2003. The oldest months's records roll out of File 990 and into File 992 on the first weekend of each month. To search all 2003 records BEGIN 990, 992, or B NEWS2003, a new OneSearch category.
***
--Connect Time joins DialUnits as pricing options on Dialog. See HELP CONNECT for information.
***
***
--SourceOne patents are now delivered to your email inbox as PDF replacing TIFF delivery. See HELP SOURCE1 for more information.
***
--Important news for public and academic libraries. See HELP LIBRARY for more information.
***
--Important Notice to Freelance Authors--
See HELP FREELANCE for more information
***
NEW FILES RELEASED
***World News Connection (File 985)
***Dialog NewsRoom - 2003 Archive (File 992)
***TRADEMARKSCAN-Czech Republic (File 680)
***TRADEMARKSCAN-Hungary (File 681)
***TRADEMARKSCAN-Poland (File 682)
***
UPDATING RESUMED
***
RELOADED
***Population Demographics -(File 581)
***CLAIMS Citation (Files 220-222)

REMOVED

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                    ***

      >>> Enter BEGIN HOMEBASE for Dialog Announcements <<<
      >>>    of new databases, price changes, etc.      <<<
                    ****
KWIC is set to 50.
HILIGHT set on as '*'
* * * * See HELP NEWS 225 for information on new search prefixes
and display codes

***                                    ***


File   1:ERIC  1966-2003/Jul 23
       (c) format only 2003 The Dialog Corporation

      Set  Items  Description
      ---  -----  -----------
Cost is in DialUnits
?b 155, 5, 55
       28jul03 13:41:38 User259876 Session D527.1
            $0.32    0.090 DialUnits File1
     $0.32  Estimated cost File1
     $0.03  TELNET
     $0.35  Estimated cost this search
     $0.35  Estimated total session cost   0.090 DialUnits


SYSTEM:OS  - DIALOG OneSearch
  File 155:MEDLINE(R)  1966-2003/Jul W4
        (c) format only 2003 The Dialog Corp.
*File 155: Medline has been reloaded and accession numbers have
changed.  Please see HELP NEWS 155.
  File   5:Biosis Previews(R)  1969-2003/Jul W3
        (c) 2003 BIOSIS
  File  55:Biosis Previews(R)  1993-2003/Jul W3
        (c) 2003 BIOSIS
*File  55: Alert feature enhanced for multiple files, duplicates
removal, customized scheduling. See HELP ALERT.

      Set  Items  Description
      ---  -----  -----------
?s ((ApoE?) or (ApoE) or (apolipoprotein (w) E)) (s) (truncated or variant or deleted)
           18306  APOE?
           13283  APOE
           62001  APOLIPOPROTEIN
         1458518  E
           19872  APOLIPOPROTEIN(W)E
          187886  TRUNCATED
          140932  VARIANT
           45326  DELETED
      S1     948  ((APOE?) OR (APOE) OR (APOLIPOPROTEIN (W) E)) (S)
                  (TRUNCATED OR VARIANT OR DELETED)
?s s1 and (hyperlipidemia or cholesterol)
             948  S1
           37792  HYPERLIPIDEMIA
          307553  CHOLESTEROL
      S2     326  S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL)
?s s2 and (vector or adenovirus)
             326  S2
          243108  VECTOR
           60862  ADENOVIRUS
      S3      23  S2 AND (VECTOR OR ADENOVIRUS)
?rd
...completed examining records
      S4      11  RD (unique items)
?t s4/3,k/all
```

4/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14430951 22464643 PMID: 12576523

***Hyp rlipidemia* in *APOE2* transgenic mice is ameliorated by a *truncated* *apoE* *variant* lacking the C-terminal domain.**

Gerritsen Gery; Kypreos Kyriakos E; Van Der Zee Andre; Teusink Bas; Zannis Vassilis I; Havekes Louis M; Van Dijk Ko Willems
Department of Human Genetics, Leiden University Medical Center, The Netherlands.

Journal of lipid research (United States) 10 16 2002, 44 (2) p408-14, ISSN 0022-2275 Journal Code: 0376606
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process

***Hyperlipidemia* in *APOE2* transgenic mice is ameliorated by a *truncated* *apoE* *variant* lacking the C-terminal domain.**

Familial dysbetalipoproteinemia associated with the apolipoprotein E2 (*APOE2*) genotype is a recessive disorder with low penetrance. We have investigated whether additional expression of full-length *APOE3*, *APOE4*, or a *truncated* *variant* of *APOE4* (*APOE4*-202) can reduce *APOE2*-associated *hyperlipidemia*. This was achieved using *adenovirus*-mediated gene transfer to mice transgenic for human *APOE2* and deficient for endogenous *Apoe* (*APOE2*.*Apoe*-/- mice). The *hyperlipidemia* of *APOE2* .*Apoe*-/- mice was readily aggravated by *APOE3* and *APOE4* overexpression. Only a very low dose of *APOE4* *adenovirus* was capable of reducing the serum *cholesterol* and triglyceride (TG) levels. Expression of higher doses of *APOE4* was associated with an increased VLDL-TG production rate and the accumulation of TG-rich VLDL in the circulation. In contrast, a high dose of *adenovirus* carrying *APOE4*-202 reduced both the *cholesterol* and TG levels in *APOE2*.*Apoe*-/- mice. Despite the absence of the C-terminal lipid-binding domain, *APOE4*-202 is apparently capable of binding to lipoproteins and mediating hepatic uptake. Moreover, overexpression of *APOE4*-202 in *APOE2*.*Apoe*-/- mice does not aggravate their hypertriglyceridemia. These results extend our previous analyses of *APOE4*-202 expression in *Apoe*-/- mice and demonstrate that *apoE4*-202 functions even in the presence of clearance-defective *apoE2*. Thus, *apoE4*-202 is a safe and efficient candidate for future therapeutic applications.

4/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10805104 97094798 PMID: 8940032

In the absence of endogenous mouse apolipoprotein E, apolipoprotein E*2(Arg-158 --> Cys) transgenic mice develop more severe hyperlipoproteinemia than apolipoprotein E*3-Leiden transgenic mice.

van Vlijmen B J; van Dijk K W; van't Hof H B; van Gorp P J; van der Zee A ; van der Boom H; Breuer M L; Hofker M H; Havekes L M
TNO Prevention and Health, Gaubius Laboratory, 2301 CE Leiden, The Netherlands. lm.havekes@pg.tno.nl

Journal of biological chemistry (UNITED STATES) Nov 29 1996, 271 (48) p30595-602, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein *E**2(Arg-158 --> Cys) (*APOE**2) transgenic mice were generated and compared to the previously generated *apolipoprotein* *E* *3-Leiden (*APOE* *3-Leiden) transgenic mice to study the variable

expression of hyperlip[redacted]oteinemia associated with t[redacted]e two *APOE* variants. In the presence of the endogenous mouse *Apoe* gene, the expression of the *APOE**3-Leiden gene resulted in slightly elevated levels of serum *cholesterol* as compared with control mice (2.7 +/- 0. 5 versus 2.1 +/- 0.2 mmol/liter, respectively), whereas the expression of the *APOE* *2(Arg-158 --> Cys) gene did not affect serum *cholesterol* levels, even after high/fat *cholesterol* feeding. The extreme *cholesterol* level usually found in *apoE*-deficient mice (*Apoe* -/- mice; 23.6 +/- 5.0 mmol/liter) could be rescued by introducing the *APOE**3-Leiden gene (*APOE**3-Leiden.*Apoe*-/-; 3.6 +/- 1. 5 mmol/liter), whereas the expression of the *APOE**2(Arg-158 --> Cys) gene in *Apoe*-/- mice minimally reduced serum *cholesterol* levels (*APOE**2.*Apoe*-/-; 16.6 +/- 2.9 mmol/liter). In vivo very low density lipoprotein (VLDL) turnover studies revealed that *APOE**2.*Apoe*-/- VLDL and *APOE**3-Leiden.*Apoe*-/- VLDL display strongly reduced fractional catabolic rates as compared with control mouse VLDL (4.0 and 6.1 versus 22.1 pools/h). In vitro low density lipoprotein (LDL) receptor binding studies using HepG2 and J774 cells showed that *APOE**2. *Apoe* -/- VLDL is completely defective in binding to the LDL receptor, whereas *APOE**3-Leiden.*Apoe* -/- VLDL still displayed a considerable binding activity to the LDL receptor. After transfection of *APOE**2.*Apoe* -/- and *APOE**3-Leiden.*Apoe*-/- mice with *adenovirus* carrying the gene for the receptor-associated protein (AdCMV-RAP), serum lipid levels strongly increased (15.3 to 42.8 and 1.4 to 15.3 mmol/liter for *cholesterol* and 5.0 to 35.7 and 0.3 to 20. 7 mmol/liter for triglycerides, respectively). This indicates that RAP-sensitive receptors, possibly the LDL receptor-related protein (LRP), mediate the plasma clearance of both *APOE**2.*Apoe*-/- and *APOE**3-Leiden. *Apoe*-/- VLDL. We conclude that in vivo the *APOE**2 *variant* is completely defective in LDL receptor binding but not in binding to LRP, whereas for the *APOE* *3-Leiden mutant both LRP and LDL receptor binding activity are only mildly affected. As a consequence of this difference, *APOE**2.*Apoe*-/- develop more severe hypercholesterolemia than *APOE**3-Leiden.*Apoe*-/- mice.

4/3,K/3 (Item 3 from file: 155)

10701081 97050338 PMID: 8895066

Hepatic gene transfer of the catalytic subunit of the apolipoprotein B mRNA editing enzyme results in a reduction of plasma LDL levels in normal and watanabe heritable hyperlipidemic rabbits.

Greeve J; Jona V K; Chowdhury N R; Horwitz M S; Chowdhury J R
Medizinische Klinik, Universitats-Krankenhaus Eppendorf, Hamburg, Germany.

Journal of lipid research (UNITED STATES) Sep 1996, 37 (9) p2001-17, ISSN 0022-2275 Journal Code: 0376606
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein (apo) B exists in two forms, the full length protein apoB-100 and the carboxyterminal-*truncated* apoB-48 that is synthesized in the intestine due to editing of the apoB mRNA which generates a premature stop codon. To determine whether gene...

... liver of rabbits reconstitutes hepatic apoB mRNA editing and how this affects the plasma levels of apoB-containing lipoproteins, we constructed an APOBEC-1 recombinant *adenovirus* (Ad APOBEC-1). After injection of Ad APOBEC-1 into normal New Zealand White (NZW) or Watanabe heritable hyperlipidemic (WHHL) rabbits, up to 50% of...

... APOBEC-1-treated NZW and WHHL rabbits contained both apoB-100 and apoB-48, whereas that from control rabbits infected with a beta-galactosidase recombinant *adenovirus* (Ad LacZ) contained exclusively apoB-100. VLDL from WHHL rabbits treated with Ad APOBEC-1 had the same

particle size, lipid composition, and content of *apolipoprotein* *E* as VLDL from Ad LacZ-infected control animals. An increase of VLDL was observed in NZW and WHHL rabbits after infection with Ad APOBEC-1...

Descriptors: Cytidine Deaminase--genetics--GE; *Gene Transfer Techniques; **Hyperlipidemia*--metabolism--ME; *Lipoproteins, LDL--blood--BL; *Liver --metabolism--ME; *RNA Editing; Adenoviridae--genetics--GE; Apolipoproteins B--metabolism--ME; Fasting; *Hyperlipidemia*--genetics--GE; Lipoproteins, HDL *Cholesterol*--blood--BL; Lipoproteins, LDL--chemistry--CH; Lipoproteins, LDL *Cholesterol*--blood--BL; Lipoproteins, VLDL--chemistry --CH; Lipoproteins, VLDL--ultrastructure--UL; Lipoproteins, VLDL *Cholesterol*--blood--BL; Rabbits; Rats; Triglycerides--blood--BL

Chemical Name: Apolipoproteins B; Lipoproteins, HDL *Cholesterol*; Lipoproteins, LDL; Lipoproteins, LDL *Cholesterol*; Lipoproteins, VLDL; Lipoproteins, VLDL *Cholesterol*; Triglycerides; apolipoprotein B-100; AICDA (activation-induced cytidine deaminase); Cytidine Deaminase; apolipoprotein B mRNA editing enzyme

4/3,K/4 (Item 4 from file: 155)

09505124 21282979 PMID: 11279066

Domains of apolipoprotein E contributing to triglyceride and *cholesterol* homeostasis in vivo. Carboxyl-terminal region 203-299 promotes hepatic very low density lipoprotein-triglyceride secretion.

Kypreos K E; van Dijk K W; van Der Zee A; Havekes L M; Zannis V I
Whitaker Cardiovascular Institute, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118, USA.

Journal of biological chemistry (United States) Jun 8 2001, 276 (23) p19778-86, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: AG12717; AG; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Domains of apolipoprotein E contributing to triglyceride and *cholesterol* homeostasis in vivo. Carboxyl-terminal region 203-299 promotes hepatic very low density lipoprotein-triglyceride secretion.

Apolipoprotein (apo) E has been implicated in *cholesterol* and triglyceride homeostasis in humans. At physiological concentration *apoE* promotes efficient clearance of *apoE*-containing lipoprotein remnants. However, high *apoE* plasma levels correlate with high plasma triglyceride levels. We have used *adenovirus*-mediated gene transfer in *apoE* -deficient mice (E(-)/-) to define the domains of *apoE* required for *cholesterol* and triglyceride homeostasis in vivo. A dose of 2 x 10(9) plaque-forming units of *apoE4*-expressing *adenovirus* reduced slightly the *cholesterol* levels of E(-)/- mice and resulted in severe hypertriglyceridemia, due to accumulation of *cholesterol* and triglyceride-rich very low density lipoprotein particles in plasma. In contrast, the *truncated* form *apoE4*-202 resulted in a 90% reduction in the plasma *cholesterol* levels but did not alter plasma triglyceride levels in the E(-)/- mice. *ApoE* secretion by cell cultures, as well as the steady-state hepatic mRNA levels in individual mice expressing *apoE4* or *apoE4* -202, were similar. In contrast, very low density lipoprotein-triglyceride secretion in mice expressing *apoE4*, but not *apoE4* -202, was increased 10-fold, as compared with mice infected with a control *adenovirus* . The findings suggest that the amino-terminal 1-202 region of *apoE4* contains the domains required for the in vivo clearance of lipoprotein remnants. Furthermore, the carboxyl-terminal 203-299 residues of *apoE* promote hepatic very low density lipoprotein-triglyceride secretion and contribute to *apoE* -induced hypertriglyceridemia.

Descriptors: Apolipoproteins E--metabolism--ME; **Cholesterol* --metabolism--ME; *Homeostasis; *Triglycerides--metabolism--ME; Adenovirida e--genetics--GE; Apolipoproteins E--blood--BL; . Apolipoproteins E

--chemistry--CH; Apoli[redacted]proteins E--genetics--GE; [redacted]e Sequence; *Cholesterol*--blood--BL; Chromatography, Liquid; DNA Primers; Liver --metabolism--ME; Mice; Mice, Knockout; RNA, Messenger--genetics--GE; RNA, Messenger--metabolism--ME; Triglycerides--blood--BL; Tumor Cells...

Chemical Name: Apolipoproteins E; DNA Primers; RNA, Messenger; Triglycerides; apolipoprotein E-4; *Cholesterol*

4/3,K/5 (Item 5 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

09476393 21250707 PMID: 11352738

The amino-terminal 1-185 domain of apoE promotes the clearance of lipoprotein remnants in vivo. The carboxy-terminal domain is required for induction of *hyperlipidemia* in normal and apoE-deficient mice.

Kypreos K E; Morani P; van Dijk K W; Havekes L M; Zannis V I

Whitaker Cardiovascular Institute, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118-2394, USA.

Biochemistry (United States) May 22 2001, 40 (20) p6027-35, ISSN 0006-2960 Journal Code: 0370623

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The amino-terminal 1-185 domain of apoE promotes the clearance of lipoprotein remnants in vivo. The carboxy-terminal domain is required for induction of *hyperlipidemia* in normal and apoE-deficient mice.

Apolipoprotein *E* (*apoE*) promotes receptor-mediated catabolism of *apoE* -containing lipoprotein remnants. Impairments in remnant clearance are associated with type III hyperlipoproteinemia and premature atherosclerosis. In humans, *apoE* plasma levels correlate with plasma triglyceride levels, suggesting that excess *apoE* may also affect plasma triglyceride levels. We have used *adenovirus*-mediated gene transfer in mice to map the domains of *apoE* required for *cholesterol* and triglyceride clearance, in vivo. *Adenovirus* expressing *apoE3* and *apoE4* at doses of (1-2) x 10(9) pfu increased plasma *cholesterol* and triglyceride levels in normal C57BL6 mice and failed to normalize the high *cholesterol* levels of *apoE* -deficient mice due to induction of hypertriglyceridemia. In contrast, an *adenovirus* expressing the *truncated* *apoE* 1-185 form normalized the *cholesterol* levels of E(-)(/)(-) mice and did not cause hypertriglyceridemia. Northern blot analysis of hepatic RNA from mice expressing the full-length and the *truncated* *apoE* forms showed comparable steady-state *apoE* mRNA levels of the full-length *apoE* forms that cause *hyperlipidemia* and the *truncated* *apoE* forms that do not cause *hyperlipidemia*. The findings suggest that the amino-terminal residues 1-185 of *apoE* are sufficient for the clearance of *apoE* -containing lipoprotein remnants by the liver, whereas domains of the carboxy-terminal one-third of *apoE* are required for *apoE*-induced *hyperlipidemia*.

Descriptors: Apolipoproteins E--physiology--PH; **Hyperlipidemia* --genetics--GE; *Lipoproteins--metabolism--ME; *Peptide Fragments --physiology--PH...; genetics--GE; Chromatography, High Pressure Liquid; Gene Deletion; Genetic Vectors--chemistry--CH; Genetic Vectors--metabolism --ME; Hypercholesterolemia--blood--BL; Hypercholesterolemia--etiology--ET; Hypercholesterolemia--genetics--GE; *Hyperlipidemia*--blood--BL; *Hyperli pidemia*--etiology--ET; Hypertriglyceridemia--blood--BL; Hypertriglyceride mia--etiology--ET; Hypertriglyceridemia--genetics--GE; Lipoproteins--blood --BL; Lipoproteins, VLDL--secretion--SE; Liver--secretion--SE; Mice; Mice, Inbred C57BL...

4/3,K/6 (Item 6 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08393734 95081713 PMI[redacted]7989859

Expression of heterologous human apolipoprotein E by J774 macrophages enhances *cholesterol* efflux to HDL3.

Mazzone T; Reardon C
Department of Medicine, Rush Medical College, Chicago, IL 60612.

Journal of lipid research (UNITED STATES) Aug 1994, 35 (8) p1345-53, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL15062; HL; NHLBI; HL39653; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Expression of heterologous human apolipoprotein E by J774 macrophages enhances *cholesterol* efflux to HDL3.

Expression of apolipoprotein (apo) E by macrophages is tightly regulated by cellular *cholesterol* content. We have investigated a potential modulating role for *apoE* on macrophage *cholesterol* homeostasis by stably transfecting the J774 macrophage, which does not express its endogenous *apoE* gene, with a human *apoE* cDNA expression *vector* and comparing *cholesterol* homeostasis in this cell line with that of a control line transfected with the neomycin resistance construct only. Incubation in serum-free medium after *cholesterol* loading produced no difference in cellular *cholesterol* content between *apoE* secreting and non-secreting J774 cells. Similarly, in serum-free medium there was no difference in the amount of radiolabeled *cholesterol* effluxed. Addition of cAMP or S58035 to *cholesterol*-loaded J774 cells did enhance efflux of radiolabeled *cholesterol* from *apoE* secreting compared to non-secreting macrophages but did not detectably alter cellular free *cholesterol* or cholesteryl ester mass. Incubation with HDL3 alone, however, significantly decreased macrophage cholesteryl ester mass compared to a 24-h incubation in serum-free medium from 10.5 +/- 3.9 to 3.2 +/- 2.0 ($P < 0.01$) in *apoE* -secreting J774 cells. During a 24-h incubation in HDL3, cholesteryl ester fell from 6.4 +/- 2.4 to 0.8 +/- 0.7 (delta = 5.6 micrograms/mg) in *apoE* -secreting cells and from 9.3 +/- 2.2 to 7.7 +/- micrograms/mg (delta = 1.6 micrograms/mg) in non-secreting cells ($P < 0.005$ *apoE*-secreting vs. non-secreting cells).(ABSTRACT *TRUNCATED* AT 250 WORDS)

Descriptors: Apolipoproteins E--secretion--SE; **Cholesterol*--metabolism --ME; *Lipoproteins, HDL--pharmacology--PD; *Macrophages--metabolism--ME; Apolipoproteins E--genetics--GE; Cell Line; *Cholesterol*--pharmacology--PD ; *Cholesterol* Esters--metabolism--ME; DNA, Complementary; Gene Transfer Techniques; Macrophages--drug effects--DE
Chemical Name: Apolipoproteins E; *Cholesterol* Esters; DNA, Complementary; Lipoproteins, HDL; *Cholesterol*

4/3,K/7 (Item 1 from file: 5)

13634769 BIOSIS NO.: 200200263590

Liver-specific overexpression of a ligand-independent ERalpha-*variant* induces hypolipidemia in male *APOE3Leiden* mice: Using genomic technology to identify potential pathways of estrogen action in the liver.

AUTHOR: d'Oliveira Christine(a); van der Zee Andre(a); Mank Eveline(a); Boer Judith M(a); den Dunnen Johan T(a); Frants Rune R(a); Havekes Louis M; Katzenellenbogen Benita S; van Dijk Ko Willems
AUTHOR ADDRESS: (a)Leiden Univ Med Ctr, Leiden**Netherlands

JOURNAL: Circulation 104 (17 Supplement):pII115 October 23, 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

Liver-specific overexpression of a ligand-independent ERal -*variant* induces hypolipidemia in male *APOE3Leiden* mice: Using genomic technology to identify potential pathways of estrogen action in the liver.
...REGISTRY NUMBERS: *CHOLESTEROL*
DESCRIPTORS:
ORGANISMS: *adenovirus* (Adenoviridae...

...gene *vector*;
CHEMICALS & BIOCHEMICALS: ...*cholesterol*--

4/3,K/8 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13634767 BIOSIS NO.: 200200263588
***Hyperlipidemia* in *APOE2* transgenic mice is aggravated by overexpression of full length *APOE3* whereas it is reduced by a *truncated* *ApoE* *variant*.**
AUTHOR: Gerritsen Gery(a); Kypreos Kyriakos E; van der Zee Andre; Zannis Vassilis I; Havekes Louis M; van Dijk Ko Willems
AUTHOR ADDRESS: (a)Leiden Univ Med Ctr, Leiden**Netherlands
JOURNAL: Circulation 104 (17 Supplement):pII114-II115 October 23, 2001
MEDIUM: print
CONFERENCE/MEETING: Scientific Sessions 2001 of the American Heart Association Anaheim, California, USA November 11-14, 2001
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English

***Hyperlipidemia* in *APOE2* transgenic mice is aggravated by overexpression of full length *APOE3* whereas it is reduced by a *truncated* *ApoE* *variant*.**
...REGISTRY NUMBERS: *CHOLESTEROL*
DESCRIPTORS:
ORGANISMS: *adenovirus* (Adenoviridae...
...gene *vector*;
...DISEASES: *hyperlipidemia*--
CHEMICALS & BIOCHEMICALS: ...*cholesterol*--
ALTERNATE INDEXING: *Hyperlipidemia* (MeSH)

4/3,K/9 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12649273 BIOSIS NO.: 200000402775
Apolipoprotein E2 (Lys146fwdarwGln) causes hypertriglyceridemia due to an *apolipoprotein* *E* *variant*-specific inhibition of lipolysis of very low density lipoproteins-triglycerides.
AUTHOR: de Beer Femke; van Dijk Ko Willems; Jong Miek C; van Vark Leonie C; van der Zee Andre; Hofker Marten H; Fallaux Frits J; Hoeben Rob C; Smelt Augustinus H M; Havekes Louis M(a)
AUTHOR ADDRESS: (a)Gaubius Laboratory, TNO-Prevention and Health, Zernikedreef 9, 2333 CK, Leiden**Netherlands
JOURNAL: Arteriosclerosis Thrombosis and Vascular Biology 20 (7):p 1800-1806 July, 2000
MEDIUM: print
ISSN: 1079-5642
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

Apolipoprotein E2 (Lys146fwdarwGln) causes hypertriglyceridemia due to an *apolipoprotein* *E* *variant*-specific inhibition of lipolysis of very

low density lipoproteins triglycerides.

ABSTRACT: The apolipoprotein E2 (Lys146fwdarwGln) variant is associated with a dominant form of familial dysbetalipoproteinemia. Heterozygous carriers of this variant have elevated levels of plasma triglycerides, *cholesterol*, and *apolipoprotein* *E* (*apoE*). It was hypothesized that the high amounts of triglycerides in the very low density lipoprotein (VLDL) fraction are due to a disturbed lipolysis of VLDL. To test this hypothesis, *apoE* knockout mice were injected with an *adenovirus* containing the human *APOE**2 (Lys146fwdarwGln) gene, Ad-E2(146), under the control of the cytomegalovirus promoter. *ApoE* knockout mice injected with an *adenovirus* *vector* encoding human *apoE3* (Ad-E3) were used as controls. Five days after *adenovirus* injection, plasma *cholesterol* levels of mice injected with a high dose of Ad-E2(146) (2X109 plaque-forming units) were not changed compared with preinjection levels, whereas in...

...dose of Ad-E2(146) (5X108 plaque-forming units) and in the groups injected with a low or a high dose of Ad-E3, plasma *cholesterol* levels were decreased 5-, 6-, and 12-fold, respectively. Plasma triglycerides were not affected in mice injected with Ad-E3. In contrast, a 7-fold...

...of plasma triglycerides (50-fold compared with Ad-E3 injection). In vitro lipolysis experiments showed that the lipolysis rate of VLDLs containing normal amounts of *apoE2* (Lys146fwdarwGln) was decreased by 54% compared with that of VLDLs containing comparable amounts of *apoE3*. The in vivo VLDL-triglyceride production rate of Ad-E2(146)-injected mice was not significantly different from that of Ad-E3-injected mice. These results demonstrate that expression of *apoE2* (Lys146fwdarwGln) causes hypertriglyceridemia due to an *apoE* *variant*-specific inhibition of the hydrolysis of VLDL-triglycerides.

DESCRIPTORS:
ORGANISMS: *adenovirus* (Adenoviridae...

...gene *vector*;
METHODS & EQUIPMENT: *adenovirus*-mediated gene transfer...
MISCELLANEOUS TERMS: ...*apolipoprotein* *E* *variant*-specific inhibition

4/3,K/10 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12561073 BIOSIS NO.: 200000314575
Sterols and inhibitors of sterol transport modulate the degradation and secretion of macrophage apoE: Requirement for the C-terminal domain.
AUTHOR: Duan Hongwei; Gu Desheng; Mazzone Theodore
AUTHOR ADDRESS: (a)Department of Medicine, Rush Medical College, 1653 W. Congress Parkway, Chicago, IL, 60612**USA
JOURNAL: Biochimica et Biophysica Acta 1484 (2-3):p142-150 April 12, 2000
MEDIUM: print
ISSN: 0006-3002
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Macrophage-derived *apoE*, produced in the vessel wall, may have important effects during atherogenesis. The production of *apoE* by macrophages can be regulated at a transcriptional level by cellular differentiation state, cytokines and sterol loading. In addition, there are post-transcriptional and post-translational loci for regulation. We have recently identified an intermediate density cell membrane fraction in which the degradation of *apoE* can be modulated by sterols. Suppressing degradation of *apoE* in this fraction by pre-incubating cells in sterols led to enhanced *apoE* secretion. In this report we

demonstrate that the suppressive effect of sterols on the degradation of newly synthesized *apoE* in this fraction depends on the presence on its C-terminal domain, by studying a macrophage cell line transfected to express a mutant form of *apoE* in which amino acids beyond amino acid 202 were *deleted*. In addition, two modulators of cellular sterol transport, progesterone and U1866A, inhibited the degradation of full-length *apoE*. In contrast, incubation of cells in the acyl-CoA: *cholesterol* acyltransferase inhibitor S58035 did not influence *apoE* degradation. As would be predicted based on the results of degradation assays, U1866A, but not S58035, increased the secretion of *apoE* from a cell line transfected to constitutively express full-length *apoE* cDNA. The effect of U1866A on *apoE* degradation, like the effect of sterol, required the presence of the *apoE* C-terminal domain. Our results indicate that alteration of intracellular sterol homeostasis by preincubation in sterols or by drugs that modify the subcellular transport of sterol, modulates the susceptibility of *apoE* to degradation and that this modulation requires the presence of C-terminal lipid binding domains.
...METHODS & EQUIPMENT: gene expression/*vector* techniques, molecular genetic method

4/3,K/11 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10697143 BIOSIS NO.: 199799318288
In the absence of endogenous mouse apolipoprotein E, apolipoprotein E*2(Arg-158 fwdarw Cys) transgenic mice develop more severe hyperlipoproteinemia than apolipoprotein E*3 Leiden transgenic mice.
AUTHOR: Van Vlijmen Bart J M; Willems Van Dijk Ko; Van't Hof H Belinda; Van Gorp Patrick J J; Van Der Zee Andre; Van Der Boom Hans; Breuer Marco L; Hofker Martin H; Havekes Louis M(a)
AUTHOR ADDRESS: (a)TNO-PG, Gaubius Lab., PO Box 2215, 2301 CE Leiden** Netherlands
JOURNAL: Journal of Biological Chemistry 271 (48):p30595-30602 1996
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: *Apolipoprotein* *E**2(Arg-158 fwdarw Cys) (*APOE**2) transgenic mice were generated and compared to the previously generated *apolipoprotein* *E**3-Leiden (*APOE**3-Leiden) transgenic mice to study the variable expression of hyperlipoproteinemia associated with these two *APOE* variants. In the presence of the endogenous mouse *Apoe* gene, the expression of the *APOE**3-Leiden gene resulted in slightly elevated levels of serum *cholesterol* as compared with control mice (2.7 +- 0.5 versus 2.1 +- 0.2 mmol/liter, respectively), whereas the expression of the *APOE**2(Arg-158 fwdarw Cys) gene did not affect serum *cholesterol* levels, even after high/fat *cholesterol* feeding. The extreme *cholesterol* level usually found in *apoE*-deficient mice (*Apoe*-/- mice; 23.6 +- 5.0 mmol/liter) could be rescued by introducing the *APOE* *3-Leiden gene (*APOE**3-Leiden-*Apoe*-/-; 3.6 +- 1.5 mmol/liter), whereas the expression of the *APOE**2(Arg-158 fwdarw Cys) gene in *Apoe* -/- mice minimally reduced serum *cholesterol* levels (*APOE**2 cntdot *Apoe*-/-; 16.6 +- 2.9 mmol/liter). In vivo very low density lipoprotein (VLDL) turnover studies revealed that *APOE**2 cntdot *Apoe*-/- VLDL and *APOE**3 cntdot Leiden cntdot *Apoe*-/- VLDL display strongly reduced fractional catabolic rates as compared with control mouse VLDL (4.0 and 6.1 versus 22.1 pools/h). In vitro low density lipoprotein (LDL) receptor binding studies using HepG2 and J774 cells showed that *APOE**2-*Apoe*-/- VLDL is completely defective in binding to the LDL receptor, whereas *APOE**3-Leiden cntdot *Apoe*-/- VLDL still displayed a considerable binding activity to the LDL receptor. After transfection of *APOE**2 cntdot *Apoe*-/- and *APOE**3-Leiden cntdot *Apoe*-/- mice with *adenovirus* carrying the gene for the receptor-associated protein (AdCMV-RAP), serum lipid levels strongly increased (15.3 to 42.8 and 1.4

to 15.3 mmol/liter for [redacted]olesterol* and 5.0 to 35.7 and [redacted] to 20.7 mmol/liter for triglycerides, respectively). This indicates that RAP-sensitive receptors, possibly the LDL receptor-related protein (LRP), mediate the plasma clearance of both *APOE**2 cntdot *Apoe*-/- and *APOE* *3-Leiden cntdot *Apoe*-/- VLDL. We conclude that in vivo the *APOE**2 *variant* is completely defective in LDL receptor binding but not in binding to LRP, whereas for the *APOE**3-Leiden mutant both LRP and LDL receptor binding activity are only mildly affected. As a consequence of this difference, *APOE**2-*Apoe*-/- develop more severe hypercholesterolemia than *APOE**3-Leiden cntdot *Apoe*-/- mice.
...REGISTRY NUMBERS: *CHOLESTEROL*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*CHOLESTEROL*
MISCELLANEOUS TERMS: ...*CHOLESTEROL*;
?ds

```
Set     Items   Description
S1        948   ((APOE?) OR (APOE) OR (APOLIPOPROTEIN (W) E)) (S) (TRUNCAT-
           ED OR VARIANT OR DELETED)
S2        326   S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL)
S3         23   S2 AND (VECTOR OR ADENOVIRUS)
S4         11   RD (unique items)
?s s2 and ((apoE3) or (apoE (w) 3))
             326  S2
            1124  APOE3
           13283  APOE
         5778040  3
             421  APOE(W)3
      S5      79  S2 AND ((APOE3) OR (APOE (W) 3))
?rd
...examined 50 records  (50)
...completed examining records
      S6      41  RD (unique items)
?s s6 not s4
              41  S6
              11  S4
      S7      34  S6 NOT S4
?t s7/3,k/all
```

7/3,K/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

14715339 22586503 PMID: 12700893

The association of the R219K polymorphism in the ATP-binding cassette transporter 1 (ABCA1) gene with coronary heart disease and hyperlipidaemia.

Evans David; Beil F Ulrich
Klinik und Poliklinik fur Innere Medizin, Medizinische Klinik I, Universitatsklinikum Hamburg-Eppendorf, Martinistrasse 52, 20246, Hamburg, Germany, evans@uke.uni-hamburg.de

Journal of molecular medicine (Berlin, Germany) (Germany) 03 26 2003, 81 (4) p264-70, ISSN 0946-2716 Journal Code: 9504370
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process

... K allele was significantly lower in those with CHD (0.16) than in those without (0.29). There were no statistically significant differences in total *cholesterol* , LDL, HDL, apoB or apoAI between carriers and non-carriers. When patients with probable secondary hypertriglyceridaemia (triglycerides >1000 mg/dl), type 2 diabetes and carriers of lipoprotein lipase polymorphisms associated with hypertriglyceridaemia were excluded, the K allele was significantly associated with reduced triglycerides but only in patients with *apoE* *3*/3 genotype. In conclusion, we provide additional evidence that the R219K polymorphism in the ABCA1 gene either

directly or as a result of linkage disequilibrium with additional functional *variant* (s), has a protective effect against CHD and is associated with lower plasma triglycerides in sub-groups of patients with hyperlipidaemia.

7/3,K/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10610011 96427615 PMID: 8830931

Apolipoprotein E1-Hammersmith (Lys146-->Asn;Arg147-->Trp), due to a dinucleotide substitution, is associated with early manifestation of dominant type III hyperlipoproteinaemia.

Hoffer M J; Niththyananthan S; Naoumova R P; Kibirige M S; Frants R R; Havekes L M; Thompson G R

MGC-Department of Human Genetics, Leiden University, The Netherlands.

Atherosclerosis (IRELAND) Aug 2 1996, 124 (2) p183-9, ISSN 0021-9150 Journal Code: 0242543

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein *E* (*apoE*) is one of the major protein constituents of chylomicron and very low density lipoprotein (VLDL) remnants and plays a central role as a ligand in the receptor-mediated uptake of these particles by the liver. Here we describe a new *variant* of *apoE*, *apoE1* -Hammersmith, which is associated with dominantly expressed type III hyperlipidaemia. The propositus, aged 26, developed tubero-eruptive xanthomas at the age of 3, her daughter developed similar lesions at age 7 but her son, aged 3, shows no clinical abnormality so far. All three cases had an *apoE3E1* phenotype and a broad beta band on lipoprotein electrophoresis. Cysteamine modification resulted in a shift of *apoE1* to the *apoE2* isoform position, indicating that the mutation leading to *apoE1*-Hammersmith occurred on an *apoE3* background. *ApoE* genotyping confirmed these results. Sequence analysis of DNA of the propositus was performed for exons 3 and 4 and revealed a dinucleotide substitution causing two...

; Adult; Anticholesteremic Agents--therapeutic use--TU; Antilipemic Agents--therapeutic use--TU; Apolipoproteins E--blood--BL; Apolipoproteins E--drug effects--DE; Child; Child, Preschool; *Cholesterol*--blood--BL; Cholestyramine--therapeutic use--TU; Cysteamine--therapeutic use--TU; DNA --analysis--AN; Electrophoresis; Exons; Genotype; Hyperlipoproteinemia Type III--blood--BL; Hyperlipoproteinemia Type III--drug...

Chemical Name: Anticholesteremic Agents; Antilipemic Agents; Apolipoproteins E; Radiation-Protective Agents; Triglycerides; Cholestyramine; Procetofen; *Cholesterol*; Cysteamine; DNA

7/3,K/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10509591 96320203 PMID: 8696955

Quantitative assessment of aortic atherosclerosis in *APOE*3* Leiden transgenic mice and its relationship to serum *cholesterol* exposure.**

Groot P H; van Vlijmen B J; Benson G M; Hofker M H; Schiffelers R; Vidgeon-Hart M; Havekes L M

Department of Vascular Biology, SmithKline Beecham Pharmaceuticals, Welwyn, Hertfordshire, UK. pieter-h-groot@sbphrd.com@inet

Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) Aug 1996, 16 (8) p926-33, ISSN 1079-5642 Journal Code: 9505803

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Quantitative assessment of aortic atherosclerosis in *APOE*3* Leiden transgenic mice and its relationship to serum *cholesterol* exposure.**

Transgenic mice overexpressing the human dysfunctional *apolipoprotein* *E* *variant*, *APOE***3* Leiden, develop *hyperlipidemia* and are highly susceptible to diet-induced atherosclerosis. In the present study, we investigated the effects of diet composition and feeding period on serum *cholesterol* exposure and the amount of atherosclerosis in the aortic sinus in these mice, using quantitative image analysis. On each of the three diets tested--a low-fat diet, a high-saturated-fat/*cholesterol* diet, and a high saturated-fat/high-*cholesterol* /0.5%-cholate diet--transgenic animals showed a marked *hyperlipidemia* compared with nontransgenic littermates. Measurement of the atherosclerotic lesion areas in cross sections of the aortic sinus in animals exposed to these three diets for...

... lesion area in transgenic mice compared with nontransgenic controls. Highly significant positive correlations were found between the log-transformed data on lesion area and serum *cholesterol* exposure (r = .82 to .85 for the 1-, 2-, and 3-month treatment groups), indicating that the *hyperlipidemia* is likely to be a major determinant in lesion formation. On the basis of these findings, we suggest that the *APOE***3* Leiden mouse represents a promising model for intervention studies with hypolipidemic and antiatherosclerotic drugs.

Descriptors: Aortic Diseases--genetics--GE; *Apolipoproteins E--genetics --GE; *Arteriosclerosis--genetics--GE; **Cholesterol*--blood--BL; * *Hyperlipidemia*--genetics--GE; Aortic Diseases--blood--BL; Aortic Diseases--pathology--PA; Apolipoproteins E--blood--BL; Arteriosclerosis --blood--BL; Arteriosclerosis--pathology--PA; *Cholesterol*, Dietary --administration and dosage--AD; Dietary Fats--administration and dosage --AD; *Hyperlipidemia*--blood--BL; Mice; Mice, Inbred C57BL; Mice, Transgenic; Sinus of Valsalva--pathology--PA

Chemical Name: Apolipoproteins E; *Cholesterol*, Dietary; Dietary Fats; apolipoprotein E-3 Leiden; *Cholesterol*

7/3,K/4 (Item 4 from file: 155)

10197022 22250791 PMID: 12364385

Accelerated atherosclerosis and calcification in vein grafts: a study in *APOE*3* Leiden transgenic mice.**

Lardenoye J H P; de Vries M R; Lowik C W G M; Xu Q; Dhore C R; Cleutjens J P M; van Hinsbergh V W M; van Bockel J H; Quax P H A

Gaubius Laboratory TNO-PG, Leiden, The Netherlands.

Circulation research (United States) Oct 4 2002, 91 (7) p577-84, ISSN 1524-4571 Journal Code: 0047103

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Accelerated atherosclerosis and calcification in vein grafts: a study in *APOE*3* Leiden transgenic mice.**

Vein grafts fail due to development of intimal hyperplasia and accelerated atherosclerosis. Many murine genetic models in which genes are overexpressed, *deleted* , or mutated have been introduced recently. Therefore, mouse models are very well suited to dissect the relative contribution of different genes in the development of accelerated atherosclerosis. In the present study, we evaluated whether accelerated atherosclerosis in human vein grafts could be mimicked in hypercholesterolemic *APOE***3* Leiden transgenic mice. Venous bypass grafting was performed in the carotid artery in *APOE***3* Leiden mice fed either a standard chow diet or a high *cholesterol*-rich diet for 4 weeks. At several time points (0 hour to 28 days), mice were euthanized and the morphology of the vein grafts was...

7/3,K/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10094213 22050546 PMID: 11861652

Reconstituted discoidal ApoE-phospholipid particles are ligands for the scavenger receptor BI. The amino-terminal 1-165 domain of ApoE suffices for receptor binding.

Li Xiaoping; Kan Horng-Yuan; Lavrentiadou Sophia; Krieger Monty; Zannis Vassilis

Section of Molecular Genetics, Whitaker Cardiovascular Institute, Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02118, USA.

Journal of biological chemistry (United States) Jun 14 2002, 277 (24) p21149-57, ISSN 0021-9258 Journal Code: 2985121R.

Contract/Grant No.: HL41484; HL; NHLBI; HL48739; HL; NHLBI; HL52212; HL; NHLBI; HL68216; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

... class B type I (SR-BI), recognizes lipid-bound apolipoprotein A-I (apoA-I) and other apolipoproteins. Here, we have used large scale cultures of *apoE*-expressing cells to purify *apoE* and prepare *apoE* containing reconstituted discoidal 1-palmitoyl-2-oleoyl-1-phosphatidylcholine (POPC)-*apoE* particles. These particles have been used to examine their binding to wild-type and mutant forms of SR-BI expressed in transfected ldlA-7 cells...

... nonspecific values measured using either control untransfected ldlA-7 cells or by inhibiting SR-BI-mediated binding with a high titer antireceptor-blocking antibody. POPC-*apoE* particles generated using *apoE2*, *apoE3*, *apoE4*, or the carboxyl-terminally *truncated* forms *apoE165*, *apoE202*, *apoE229*, and *apoE259* all bound tightly to wild-type SR-BI with similar affinities (K(d) = 35-45 microg/ml). Binding was nearly abolished in a cell line...

... double mutant form of SR-BI that is unable to bind native high density lipoprotein but binds low density lipoprotein normally. The findings establish that *apoE* is a ligand for SR-BI and that the receptor binding domain is located in the amino-terminal 1-165-region of the protein. SR-BI-*apoE* interactions may contribute to *cholesterol* homeostasis in tissues and cells expressing SR-BI that are accessible to *apoE*-containing lipoproteins.

7/3,K/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09914100 21823299 PMID: 11834530

Postprandial plasma ApoB-48 levels are influenced by a polymorphism in the promoter of the microsomal triglyceride transfer protein gene.

Lundahl Bjorn; Hamsten Anders; Karpe Fredrik

Atherosclerosis Research Unit, King Gustaf V Research Institute, Department of Medicine, Karolinska Hospital, Stockholm, Sweden.

Arteriosclerosis, thrombosis, and vascular biology (United States) Feb 1 2002, 22 (2) p289-93, ISSN 1524-4636 Journal Code: 9505803

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

The microsomal triglyceride transfer protein (MTP) plays a key role in

the secretion of apolipoprotein B (apoB)-containing lipoproteins. The rare *variant* of a functional polymorphism in the promoter region of the MTP gene has been associated with elevated transcriptional activity of the gene in vitro (MTP...

... of this polymorphism, the appearance in plasma of apoB-48 after a meal intake. A total of 12 homozygous carriers of the rare MTP-493T *variant* were identified from a population-based screening of 50-year-old healthy white men. All subjects were of the *apoE3*/3 genotype. Along with 48 baseline well-matched heterozygotes (n=24) plus homozygotes (n=24) for the common *variant* , they were given a standardized oral fat meal. Postprandial plasma concentrations of apoB-48 were determined by the combination of density gradient ultracentrifugation and analytical SDS-PAGE. The postprandial plasma concentrations of triglycerides did not differ between the groups, but homozygous carriers of the rare MTP-493T *variant* showed a >100% greater increase in apoB-48 in the smallest (Svedberg flotation rate constant 20 to 60) triglyceride-rich lipoprotein fraction (P=0.005...

; Analysis of Variance; Area Under Curve; Dietary Fats--administration and dosage--AD; Genotype; Heterozygote; Lipoproteins, LDL *Cholesterol* --blood--BL; Middle Age; Population Surveillance; Reference Values; Sweden; Triglycerides--blood--BL

Chemical Name: Apolipoproteins B; Carrier Proteins; Dietary Fats; Lipoproteins, LDL *Cholesterol*; Triglycerides; apolipoprotein B-100; apolipoprotein B-48; microsomal triglyceride transfer protein

7/3,K/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09232513 20544588 PMID: 11095479

Familial splenomegaly: macrophage hypercatabolism of lipoproteins associated with apolipoprotein E mutation [apolipoprotein E (delta149 Leu)].

Nguyen T T; Kruckeberg K E; O'Brien J F; Ji Z S; Karnes P S; Crotty T B; Hay I D; Mahley R W; O'Brien T

Divisions of Endocrinology, Mayo Clinic and Foundation, Rochester, Minnesota 55905, USA. nguyen.tu@mayo.edu

Journal of clinical endocrinology and metabolism (UNITED STATES) Nov 2000, 85 (11) p4354-8, ISSN 0021-972X Journal Code: 0375362

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Splenomegaly with sea-blue histiocytes is not associated with dyslipidemia, except in severe cases of hypertriglyceridemia, Tangier disease, or lecithin *cholesterol* acyltransferase deficiency. We describe two kindreds in which the sea-blue histiocyte syndrome was associated with an *apoE* *variant* in the absence of severe dyslipidemia. Both patients presented with mild hypertriglyceridemia and splenomegaly. After splenectomy both patients developed severe hypertriglyceridemia. Pathological evaluation of the spleen revealed the presence of sea-blue histiocytes. A mutation of *apoE* was demonstrated, with a 3-bp deletion resulting in the loss of a leucine at position 149 in the receptor-binding region of the *apoE* molecule [*apoE* (delta149 Leu)]. Although both probands were unrelated, they were of French Canadian ancestry, suggesting the possibility of a founder effect. In summary, we describe two...

... mildly elevated serum triglyceride concentrations that markedly increased after splenectomy. In addition, we provide evidence linking the syndrome to an inherited dominant mutation in the *apoE* gene, a 3-bp deletion on the background of an *apoE* *3* allele that causes a derangement in lipid metabolism and leads to splenomegaly in the absence of severe hypertriglyceridemia.

7/3,K/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09095691 20393463 PMID: 10939469

Phenotyping apolipoprotein E*3-leiden transgenic mice by two-dimensional polyacrylamide gel electrophoresis and mass spectrometric identification.

Skehel J M; Schneider K; Murphy N; Graham A; Benson G M; Cutler P; Camilleri P

Department of Analytical Sciences, SmithKline Beecham Pharmaceuticals, Harlow, Essex, UK. mark j skehel@sbphrd.com

Electrophoresis (GERMANY) Jul 2000, 21 (12) p2540-5, ISSN 0173-0835 Journal Code: 8204476

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein *E* (*ApoE*) plays an important role in *cholesterol* and triglyceride metabolism, being one of the major structural components of chylomicrons and very low density lipoprotein (VLDL) remnants. *ApoE* functions as a ligand in the receptor-mediated uptake of these remnants from the blood by the liver. A *variant* form of *ApoE*, *apolipoprotein* *E* *3-Leiden, shows reduced affinity for the low density lipoprotein (LDL) receptor, and results in the dominant expression of type III hyperlipoproteinemia. Two-dimensional electrophoresis (2-DE) has been used to characterise protein expression in serum samples from control and transgenic mice expressing the human *ApoE***3*-Leiden mutation, fed a *cholesterol* -rich diet, and transgenic mice fed a normal diet. For the identification of proteins, single silver-stained spots were excised from the 2-DE gels...

... digestion. Extracted peptides were analysed by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF-MS). This proteomic approach has enabled the *ApoE***3*-Leiden *variant* to be positioned in a 2-DE separation of serum proteins, and has identified changes in the expression of haptoglobin, indicating that this protein may ...

; Amino Acid Sequence; Apolipoproteins E--classification--CL; Apolipoproteins E--genetics--GE; *Cholesterol*, Dietary--metabolism--ME; Electrophoresis, Gel, Two-Dimensional--methods--MT; Mice; Mice, Transgenic; Molecular Sequence Data; Phenotype; Spectrometry, Mass, Matrix-Assisted Laser Desorption-Ionization--methods--MT

Chemical Name: Apolipoproteins E; *Cholesterol*, Dietary; apolipoprotein E-3 Leiden

7/3,K/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08825047 20108551 PMID: 10642431

Apolipoprotein E genetic polymorphism, serum lipoproteins, and breast cancer risk.

Moysich K B; Freudenheim J L; Baker J A; Ambrosone C B; Bowman E D; Schisterman E F; Vena J E; Shields P G

Department of Cancer Prevention, Epidemiology, and Biostatistics, Roswell Park Cancer Institute, Buffalo, New York 14263, USA. kmoysich@sc3103.med.buffalo.edu

Molecular carcinogenesis (UNITED STATES) Jan 2000, 27 (1) p2-9, ISSN 0899-1987 Journal Code: 8811105

Document type: Journal Article; Multicenter Study
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein *E* poE*) is a polymorphic gene involved in lipid metabolism with three common *variant* alleles (epsilon2, epsilon3, and epsilon4). The epsilon4 allele has been associated with elevated levels of *cholesterol* as well as greater risk of coronary heart disease and Alzheimer's disease. In this case-control study we examined whether *apoE* genotype affected the association between serum lipids and breast cancer risk. In a subset of a study in western New York, 260 women with incident, primary breast cancer and 332 community controls were interviewed and provided blood samples. Polymerase chain reaction-restriction fragment length polymorphism analyses of the *apoE* polymorphism were performed. Participants were classified as *apoE2* (epsilon2, epsilon2 or epsilon2, epsilon3), *apoE3* (epsilon3, epsilon3), or *apoE4* (epsilon4, epsilon4 or epsilon4, epsilon3). No unconditional logistic regression was used to compute adjusted odds ratios (ORs) and 95% confidence intervals (CI). Compared with women with the *apoE3* genotype, there were no associations with risk for women with the *apoE2* (OR=1.0; 95% CI=0. 91-1.64) or *apoE4* genotype (OR=0.97; 95% CI=0.63-1.54). Higher serum levels of total *cholesterol*, HDL *cholesterol*, and LDL *cholesterol* were not associated with risk, either in the total sample or among subgroups of women defined by *apoE* genotype. Women with the highest serum triglyceride levels had an increase in risk (OR=1.63; 95% CI=1. 03-2.59) compared to women with the lowest levels. This effect was not apparent among women with the *apoE2* or *apoE3* genotype, but much stronger among women with the *apoE4* genotype (OR=4.69; 95% CI=1. 49-14.7). These data suggest that the *apoE4* genotype may modify the association between serum triglycerides and breast cancer risk. Copyright 2000 Wiley-Liss, Inc.

; Aged; Case-Control Studies; Caucasoid Race; *Cholesterol*--blood--BL; *Cholesterol*, Dietary; Dietary Fats; Genotype; Lipoproteins, HDL--blood --BL; Lipoproteins, LDL--blood--BL; Middle Age; New York--epidemiology--EP; Risk Factors; Triglycerides--blood--BL

Chemical Name: Apolipoproteins E; *Cholesterol*, Dietary; Dietary Fats; Lipoproteins; Lipoproteins, HDL; Lipoproteins, LDL; Triglycerides; *Cholesterol*

7/3,K/10 (Item 10 from file: 155)

08703068 95391673 PMID: 7662677

Comparison of lipid-binding and lecithin:*cholesterol* acyltransferase activation of the amino- and carboxyl-terminal domains of human apolipoprotein E3.

De Pauw M; Vanloo B; Weisgraber K; Rosseneu M

Department of Biochemistry, Faculty of Medicine, University of Gent, Belgium.

Biochemistry (UNITED STATES) Aug 29 1995, 34 (34) p10953-66, ISSN 0006-2960 Journal Code: 0370623

Contract/Grant No.: HL 41633; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Comparison of lipid-binding and lecithin:*cholesterol* acyltransferase activation of the amino- and carboxyl-terminal domains of human apolipoprotein E3.

To extend the characterization of the functional domains of *apolipoprotein* *E* (*apoE*), the amino-(residues 1-191, 22-kDa) and carboxyl-terminal (residues 216-299, 10-kDa) fragments were tested for lipid binding and lecithin:*cholesterol* acyltransferase (LCAT) activation. A disulfide bond linking helices 2 and 3 of the four-helix bundle amino-terminal domain was introduced by mutating threonine-57 to cysteine (Thr57-->Cys) in *apoE3* (cysteine at position 112) to determine the influence of the disulfide bond on the properties of this domain. Lipid-binding properties were determined by the...

... DMPC) and dipalmitoylphosphatidylcholine, assessed by measuring decreases in turbidity as a function of temperature. The results demonstrate that the relative lipid binding efficiencies were intact *apoE3* approximately 10-kDa fragment > 22-kDa fragment > Thr57-->Cys *variant* . In addition, free, non-lipid-associated protein was observed with the two 22-kDa fragments but not with intact *apoE3* or the 10-kDa fragment. The transition temperatures determined by fluorescence polarization were higher for the DMPC complexes with intact *apoE3* and with 22- and 10-kDa fragments (25.5 degrees C) than with the 22-kDa Thr57-->Cys *variant* (23.5 degrees C), suggesting that the *variant* fragment possessed the lowest affinity for lipid. Attenuated total reflection infrared measurements of the complexes indicated that the long axes of the alpha-helices of the various *apoE* forms were parallel to the acyl chains of the phospholipid bilayer.(ABSTRACT *TRUNCATED* AT 250 WORDS)

7/3,K/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08601708 95290025 PMID: 7772075

The relationship of APOE polymorphism and *cholesterol* levels in normoglycemic and diabetic subjects in a biethnic population from the San Luis Valley, Colorado.

Kamboh M I; Aston C E; Hamman R F
Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh, PA 15261, USA.

Atherosclerosis (IRELAND) Jan 20 1995, 112 (2) p145-59, ISSN 0021-9150 Journal Code: 0242543
Contract/Grant No.: DK30747; DK; NIDDK; HL 44672; HL; NHLBI; HL49074; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The relationship of APOE polymorphism and *cholesterol* levels in normoglycemic and diabetic subjects in a biethnic population from the San Luis Valley, Colorado.

We have determined *apolipoprotein* *E* (*apoE* = protein, *APOE* = gene) polymorphism and its relationship with total *cholesterol* (TC), low density lipoprotein *cholesterol* (LDL-C), high density lipoprotein *cholesterol* (HDL-C) and triglyceride levels in normoglycemic Hispanics (n = 446) and non-Hispanic whites (NHWs) (n = 659) as well as in diabetic Hispanics (n = 235...

... group, and within each group men and women were analyzed separately; women were further categorized into pre- and post-menopausal status. The distribution of the *APOE* genotype pattern was comparable between the NHW normoglycemics and diabetics but it was significantly different among Hispanic normoglycemics and diabetics ($P < 0.005$). In the normoglycemic sample the *APOE* allele frequencies were significantly different between the two ethnic groups: the *APOE**2 (0.09 vs. 0.05; $P < 0.01$) and *APOE**4 (0.15 vs. 0.09; $P < 0.002$) allele frequencies were higher while the *APOE**3* (0.76 vs. 0.86; $P < 0.0001$) allele frequency was lower in NHWs than in Hispanics. Significant variability among the three common *APOE* genotypes (3-2, 3-3, and 4-3) was observed for TC and LDL-C in normoglycemic Hispanic women ($P = 0.09$ and $P = 0.03$) but not in Hispanic men. In normoglycemic NHWs, however, significant mean differences among *APOE* genotypes were observed for TC and LDL-C in both women ($P < 0.0001$ and $P < 0.0001$) and men ($P = 0.009$ and $P = 0.01$). In Hispanic females, the *APOE* polymorphism accounted for 5.6% and 7.6% of the phenotypic variance for TC and LDL-C, respectively. In NHW females, the *APOE* polymorphism explained 10.2% of the phenotypic variance for TC and LDL-C, and in NHW males these values were 6.2% and 7.5%, respectively. There was no evidence of physiologic interaction between the *APOE* polymorphism and menopause status in affecting TC and LDL-C in NHW women ($P = 0.65$ and $P = 0.55$) but a

suggestion of interaction.

... TC and LDL-C (P = 0.11 and 0.07). After the Hispanic women were stratified into pre- and postmenopausal groups, the effect of the *APOE* polymorphism on TC and LDL-C was significant only in the premenopausal group. Among diabetics, no significant effect of the *APOE* polymorphism was seen on *cholesterol* levels.(ABSTRACT *TRUNCATED* AT 400 WORDS)

Descriptors: Apolipoproteins E--genetics--GE; **Cholesterol*--blood--BL; *Diabetes Mellitus, Non-Insulin-Dependent--ethnology--EH; *Hispanic Americans...; genetics--GE; Diabetes Mellitus, Non-Insulin-Dependent--blood --BL; Diabetes Mellitus, Non-Insulin-Dependent--genetics--GE; Gene Frequency; Genotype; Hispanic Americans--genetics--GE; Lipoproteins, HDL *Cholesterol*--blood--BL; Lipoproteins, LDL *Cholesterol*--blood--BL; Middle Age; Molecular Sequence Data; Polymorphism (Genetics); Postmenopause ; Premenopause; Triglycerides--blood--BL

Chemical Name: Apolipoproteins E; Blood Glucose; Lipoproteins, HDL *Cholesterol*; Lipoproteins, LDL *Cholesterol*; Triglycerides; *Cholesterol*

7/3,K/12 (Item 12 from file: 155)

08580647 95268949 PMID: 7749827

***Cholesterol* absorption and metabolism and LDL kinetics in healthy men with different apoprotein E phenotypes and apoprotein B Xba I and LDL receptor Pvu II genotypes.**

Gylling H; Kontula K; Miettinen T A
Second Department of Medicine, University of Helsinki, Finland.

Arteriosclerosis, thrombosis, and vascular biology (UNITED STATES) Feb 1995, 15 (2) p208-13, ISSN 1079-5642 Journal Code: 9505803
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

***Cholesterol* absorption and metabolism and LDL kinetics in healthy men with different apoprotein E phenotypes and apoprotein B Xba I and LDL receptor Pvu II genotypes.**

Apoprotein (apo) E, apoB Xba I, and LDL receptor gene Pvu II polymorphisms are associated with LDL *cholesterol* level, but little is known about *cholesterol* and LDL metabolism in subjects with the latter two genetic polymorphisms alone or in combination with different *apoE* phenotypes. We studied *cholesterol* absorption efficiency, *cholesterol* and bile acid synthesis, and LDL apoB kinetics in 52 healthy men and related the metabolic results to the apoB Xba I and LDL receptor Pvu II restriction fragment length polymorphism (RFLP) and *apoE* phenotypes. New findings were as follows. ApoB Xba I polymorphism was not associated with the metabolic variables of *cholesterol*, but LDL receptor Pvu II RFLP was associated with fractional catabolic rate for LDL apoB, *cholesterol* absorption, and *cholesterol* and bile acid synthesis. *ApoE* polymorphism exerted the most powerful effect on the LDL *cholesterol* concentration, so that the *apoE2* subjects had the lowest LDL *cholesterol* and apoB levels and *cholesterol* absorption, and the highest fractional catabolic rate and bile acid and *cholesterol* synthesis compared with the *apoE3* or especially *apoE4* phenotypes in different genetic combinations. In multiple stepwise regression analysis with LDL *cholesterol* as the dependent and the genetic and metabolic parameters as the independent variables, 47.0% (n = 35, P < .001) of the variability of LDL *cholesterol* was explained by the *apoE* polymorphism, 7.1% (P < .05) by the LDL receptor Pvu II RFLP, and 11.3% (P < .01) by bile acid synthesis, while the contribution of the apoB Xba I RFLP was nonsignificant.(ABSTRACT *TRUNCATED* AT 250 WORDS)

Descriptors: Apolipoproteins B--genetics--GE; *Apolipoproteins E --chemistry--CH; **Cholesterol*--metabolism--ME; *Lipoproteins, LDL --metabolism--ME; *Polymorphism (Genetics); *Receptors, LDL--genetics--GE

Chemical Name: Apolipoproteins B; Apolipoproteins E; Bile Acids and Salts ; Lipoproteins, LDL; Receptors, LDL; *Cholesterol*; DNA

7/3,K/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08533854 95222140 PMID: 7706948
Identification and characterization of a novel *apolipoprotein* *E* *variant* , apolipoprotein E3' (Arg136-->His): association with mild dyslipidemia and double pre-beta very low density lipoproteins.
Minnich A; Weisgraber K H; Newhouse Y; Dong L M; Fortin L J; Tremblay M; Davignon J
Clinical Research Institute of Montreal, P.Q., Canada.
Journal of lipid research (UNITED STATES) Jan 1995, 36 (1) p57-66, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL41633; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Identification and characterization of a novel *apolipoprotein* *E* *variant* , apolipoprotein E3' (Arg136-->His): association with mild dyslipidemia and double pre-beta very low density lipoproteins.
Apolipoprotein (apo) E mediates the removal of chylomicron and VLDL remnants from plasma. In a proband with mild *hyperlipidemia* and a family history of premature coronary artery disease, we have identified a new mutant of *apoE* with an isoelectric point close to but distinct from that of *apoE3*. Sequencing of the *apoE* gene from this subject (JB) revealed that the subject was heterozygous for a G to A substitution in codon 136, resulting in the substitution of histidine for arginine; therefore, we have designated this isoform *apoE3* ' (Arg136-->His). Examination of the proband's kindred revealed that the nine carriers (all heterozygotes) of the *variant* isoform displayed a twofold elevation in the concentration of very low density lipoprotein (VLDL) *cholesterol* (40 +/- 8 mg/dl) and triglyceride (109 +/- 19) compared to the nine noncarriers (19 +/- 3 and 55 +/- 13, respectively). In all carriers, the VLDL displayed an abnormal double pre-beta pattern upon electrophoresis. The low density lipoprotein receptor-binding activity of purified *apoE3* ' (Arg136-->His) when complexed with DMPC was slightly defective (80% of the activity of normal *apoE*). The mutant *apoE* also displayed a reduced affinity for heparin compared to *apoE3*. As both of these biochemical parameters are known to be important in VLDL clearance, the defects associated with this *variant* are likely responsible for the increase in VLDL observed in carriers. None of the carriers displayed clinical features of type III hyperlipoproteinemia, suggesting that the relatively mild dyslipoproteinemic phenotype associated with this *variant* might be associated with recessive expression of this disorder. However, the abnormal VLDL phenotype appears to be dominantly expressed.
Descriptors: Apolipoproteins E--genetics--GE; *Arginine--genetics--GE; *Histidine--genetics--GE; **Hyperlipidemia*--genetics--GE; *Lipoproteins, VLDL--blood--BL; Adult; Base Sequence; DNA--chemistry--CH; Electrophoresis, Agar Gel; Hydrogen-Ion Concentration; *Hyperlipidemia*--blood--BL; Isoelectric Focusing; Molecular Sequence Data; Mutation; Pedigree; Phenotype

7/3,K/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08447278 95135449 PMID: 7833947
Genetic heterogeneity of apolipoprotein E and its influence on plasma lipid and lipoprotein levels.
de Knijff P; van den Maagdenberg A M; Frants R R; Havekes L M

TNO Institute of Prevention and Health Research, Gaubius Laboratory, Leiden, The Netherlands.
Human mutation (UNITED STATES) 1994, 4 (3) p178-94, ISSN 1059-7794 Journal Code: 9215429
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein *E* (*apoE*) is one of the major protein constituents of chylomicron and very-low-density lipoprotein (VLDL) remnants and plays a central role as a ligand in the receptor-mediated uptake of these particles by the liver. Including the most common *variant*, *apoE3*, 30 *apoE* variants have been characterized. At present, 14 *apoE* variants have been found to be associated with familial dysbetalipoproteinemia, a genetic lipid disorder characterized by elevated plasma *cholesterol* and triglyceride levels and an increased risk for atherosclerosis. Seven *apoE* variants were found to be associated with other forms of hyperlipoproteinemia. This report presents an overview of all currently known *apoE* variants and their effects on lipoprotein metabolism.
; Alleles; Amino Acid Sequence; Base Sequence; DNA--genetics--GE; Gene Frequency; *Hyperlipidemia*--blood--BL; *Hyperlipidemia*--genetics--GE; Hyperlipoproteinemia Type III--blood--BL; Hyperlipoproteinemia Type III --diagnosis--DI; Hyperlipoproteinemia Type III--genetics--GE; Molecular Sequence Data; Mutation

7/3,K/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08346634 95034605 PMID: 7947593
Plasma lipoproteins in familial dysbetalipoproteinemia associated with apolipoproteins E2(Arg158-->Cys), E3-Leiden, and E2(Lys146-->Gln), and effects of treatment with simvastatin.
Zhao S P; Smelt A H; Van den Maagdenberg A M; Van Tol A; Vroom T F; Gevers Leuven J A; Frants R R; Havekes L M; Van der Laarse A; Van 't Hooft F M
Department of Cardiology, Medical Faculty, University of Leiden, Netherlands.
Arteriosclerosis and thrombosis - a journal of vascular biology / American Heart Association (UNITED STATES) Nov 1994, 14 (11) p1705-16, ISSN 1049-8834 Journal Code: 9101388
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

...analyzed in detail the plasma lipoprotein profiles of 18 patients with familial dysbetalipoproteinemia (FD) who had apolipoprotein (apo) E2(Arg158-->Cys) homozygosity (the E2-158 *variant*, n = 6), *apoE3*-Leiden heterozygosity (the E3-Leiden *variant*, n = 6), or *apoE2*(Lys146-->Gln) heterozygosity (the E2-146 *variant*, n = 6), with average plasma *cholesterol* concentrations of 8.99 +/- 1.34 mmol/L, 9.29 +/- 1.55 mmol/L, and 8.46 +/- 1.10 mmol/L, respectively. No significant differences...

... and intermediate-density lipoprotein (IDL) and a higher cholesteryl ester content of VLDL1 and VLDL2 than in 6 normolipidemic control subjects with an average plasma *cholesterol* concentration of 5.90 +/- 0.53 mmol/L. Major differences between the plasma lipoprotein profiles of patients with the E2-158 *variant*, the E3-Leiden *variant*, and the E2-146 *variant* and the normolipidemic control subjects were in IDL *cholesterol* concentration (1.70 +/- 0.26, 1.50 +/- 0.26, 1.05 +/- 0.36, and 0.47 +/- 0.14 mmol/L, respectively), LDL *cholesterol* concentration (1.83 +/- 0.50, 3.09 +/- 0.32, 3.79 +/- 0.76, and 3.77 +/- 0.56 mmol/L, respectively), and the molar ratio of IDL *cholesterol* to LDL *cholesterol* (0.98 +/- 0.28, 0.48 +/- 0.04, 0.28 +/- 0.09, and 0.12 +/- 0.03, respectively). After 10 weeks of

simvastatin treatment t[redacted] concentrations of plasma *ch[redacted]sterol*, VLDL2 *cholesterol*, IDL *cholesterol*, and LDL *cholesterol* in 3 patients with the E2-158 *variant* fell significantly, by 46%, 56%, 53%, and 48%, respectively; they also fell in 3 patients with the E3-Leiden *variant*, by 48%, 54%, 57%, and 52%, respectively, and in 3 patients with the E2-146 *variant* , by 38%, 55%, 46%, and 35%, respectively. Simvastatin therapy lowered plasma activity of cholesteryl ester transfer protein but had no significant effect on plasma activity of lecithin:*cholesterol* acyltransferase. It is concluded that patients with FD due to various *apoE* variants have different lipoprotein profiles, mainly with regard to IDL and LDL levels, although they have a number of similar features of dysbetalipoproteinemia. Simvastatin therapy effectively reduced the plasma concentrations of total *cholesterol*, VLDL2 *cholesterol*, IDL *cholesterol*, and LDL *cholesterol* in the three groups of patients studied. It is proposed that *apoE*-dependent defects of the conversion of IDL to LDL may be an important mechanism in the pathophysiology of FD.

Chemical Name: Apolipoproteins E; Carrier Proteins; Lipoproteins; apolipoprotein E-2; apolipoprotein E-3; *cholesterol* ester transfer proteins; Lovastatin; Simvastatin; Phosphatidylcholine-Sterol O-Acyltransferase

7/3,K/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08281623 94347689 PMID: 8068601

Impact of apolipoprotein E polymorphism on lipoproteins and risk of myocardial infarction. The ECTIM Study.

Luc G; Bard J M; Arveiler D; Evans A; Cambou J P; Bingham A; Amouyel P; Schaffer P; Ruidavets J B; Cambien F; et al

SERLIA and INSERM U325, Pasteur Institute of Lille, France.

Arteriosclerosis and thrombosis - a journal of vascular biology / American Heart Association (UNITED STATES) Sep 1994, 14 (9) p1412-9, ISSN 1049-8834 Journal Code: 9101388

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

... MONICA project: Belfast (Northern Ireland) and Lille, Strasbourg, and Toulouse (France). Control subjects (n = 722) were randomly selected from the regional populations. The distribution of *apoE* phenotypes was significantly different across the four control samples (P = .04), with a higher frequency of the epsilon 4 allele in Belfast (14.3%) than in Toulouse (8.2%). The association of *apoE* polymorphism with biological measurements was studied in the control groups (n = 640) after men with coronary heart disease or those taking hypolipidemic drugs were omitted, with the *apoE3* /3 phenotype as a reference after adjustment for concomitant factors. Individuals carrying the epsilon 2 allele had lower levels of plasma *cholesterol*, low-density lipoprotein *cholesterol* (LDL-C), and apoB and higher levels of triglycerides, very-low-density lipoprotein *cholesterol* (VLDL-C), apoC-III, *apoE* , lipoprotein (Lp) C-III:B, and Lp E:B. However, the effect of the epsilon 2 allele on triglyceride, VLDL-C, *apoE* , and Lp E:B parameters was heterogeneous across the populations.(ABSTRACT *TRUNCATED* AT 250 WORDS)

; Adult; Alleles; Apolipoproteins--metabolism--ME; Apolipoproteins B --metabolism--ME; *Cholesterol*--blood--BL; Lipoproteins, LDL *Cholesterol* --blood--BL; Lipoproteins, VLDL *Cholesterol*--blood--BL; Middle Age; Myocardial Infarction; Risk Factors; Triglycerides--blood--BL

Chemical Name: Apolipoproteins; Apolipoproteins B; Apolipoproteins E; Lipoproteins; Lipoproteins, LDL *Cholesterol*; Lipoproteins, VLDL *Cholesterol*; Triglycerides; *Cholesterol*

7/3,K/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08218772 94284725 PMID: 8014576

Altered lipoprotein metabolism in transgenic mice expressing low levels of a human receptor-binding-defective *apolipoprotein* *E* *variant*.

Fazio S; Horie Y; Simonet W S; Weisgraber K H; Taylor J M; Rall S C

Gladstone Institute of Cardiovascular Disease, University of California, San Francisco 94141-9100.

Journal of lipid research (UNITED STATES) Mar 1994, 35 (3) p408-16, ISSN 0022-2275 Journal Code: 0376606

Contract/Grant No.: HL47660; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Altered lipoprotein metabolism in transgenic mice expressing low levels of a human receptor-binding-defective *apolipoprotein* *E* *variant*.

Transgenic mouse lines were produced that expressed low levels of a receptor-binding-defective *variant* of human apolipoprotein (apo) E, *apoE*(Arg112, Cys142). In transgenic mice, the human *apoE* was produced only by the kidney, whereas endogenous mouse *apoE* was produced mainly by the liver. The plasma concentration of the transgenic protein was about half that of endogenous *apoE*. The expression of transgenic *apoE* did not affect total plasma *cholesterol* and triglyceride levels, but the distribution of the human *variant* differed from that of endogenous *apoE* in the intermediate size and density range, where the transgenic protein accumulated selectively. Immunoblots of agarose gels of lipoprotein fractions showed that the transgenic protein occurred primarily on large alpha-migrating particles (HDL1). This phenomenon was not observed in transgenic mice expressing normal human *apoE*-*3*, which distributed like endogenous *apoE*, suggesting that the defective *apoE* *variant* perturbed HDL1 metabolism. In mice fed a high-fat, high-*cholesterol* diet, the transgenic *apoE* associated primarily with the apoB-containing lipoproteins. A significantly higher increase in very low density lipoprotein *cholesterol* was observed in fat-fed transgenics compared to fat-fed nontransgenic mice, suggesting a metabolic perturbation of apoB-containing lipoproteins. Thus, the receptor-binding-defective *variant*, *apoE* (Arg112, Cys142), expressed at low levels by the kidney, alters lipoprotein metabolism in transgenic mice, presumably by interfering with *apoE*-mediated removal of the lipoproteins from circulation.

; Apolipoproteins E--metabolism--ME; Blotting, Southern; Blotting, Western; *Cholesterol*--blood--BL; Gene Expression; Immunoblotting; Lipoproteins, HDL--blood--BL; Mice; Mice, Inbred ICR; Mice, Transgenic; Particle Size; Triglycerides--blood--BL

Chemical Name: Apolipoproteins E; Lipoproteins; Lipoproteins, HDL; Triglycerides; *Cholesterol*

7/3,K/18 (Item 18 from file: 155)

08164573 94230449 PMID: 8175773

Variable heparan sulfate proteoglycan binding of apolipoprotein E variants may modulate the expression of type III hyperlipoproteinemia.

Ji Z S; Fazio S; Mahley R W

Gladstone Institute of Cardiovascular Disease, Cardiovascular Research Institute, San Francisco, California 94141-9100.

Journal of biological chemistry (UNITED STATES) May 6 1994, 269 (18) p13421-8, ISSN 0021-9258 Journal Code: 2985121R

Contract/Grant No.: HL41633; HL; NHLBI

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

... surface-bound remn s are believed to be inte lized by their interaction with the low density lipoprotein (LDL) receptor-related protein or by the LDL receptor. *Cholesterol*-induced rabbit beta-very low density lipoproteins (beta-VLDL) enriched in human *apoE3* display 4-5-fold enhanced binding to cultured cells. The present study attempts to determine whether recessive versus dominant type III hyperlipoproteinemia might be explained, at least in part, by a variable interaction of the mutant forms of *apoE* with the HSPG and impaired uptake. The beta-VLDL+*apoE2* (Arg158-->Cys), which is associated with recessive type III hyperlipoproteinemia, bound more poorly than beta-VLDL+*apoE3* but still possessed significant enhanced binding (approximately 2-2.5-fold compared with beta-VLDL without added *apoE*) to HepG2 and McA-RH7777 cells. In comparison, beta-VLDL+*apoE*(Arg142-->Cys), beta-VLDL+*apoE*(Arg145-->Cys), and beta-VLDL+*apoE* -Leiden, which are associated with dominant type III hyperlipoproteinemia, bound more poorly. This same hierarchy of binding and uptake was determined by [14C]oleate incorporation into cholesteryl esters in LDL receptor-negative cells and by secretion of *apoE3* and the *variant* *apoE* forms from McA-RH7777 cells. Furthermore, the enhanced binding of the *apoE*-enriched beta-VLDL was almost totally inhibited by heparinase treatment of the cells, and the basal binding activity was inhibited by 80-90% following addition of an LDL receptor antibody capable of blocking receptor-ligand interaction. The beta-VLDL enriched in *apoE* or *apoE*-dimyristoylphosphatidylcholine complexes bound to isolated HSPG from McA-RH7777 cells or the rat liver to a very similar degree. Likewise, the binding of beta-VLDL plus the various forms of *apoE* to the LDL receptor-related protein on ligand blots paralleled the results of other studies. In conclusion, all of the type III hyperlipoproteinemic *apoE* variants are defective in displaying enhanced binding to HSPG and in the cellular uptake initiated by HSPG. However, *apoE2*(Arg158-->Cys) displayed more activity than the variants associated with the dominant forms of type III hyperlipoproteinemia. The hierarchy of binding and uptake was as follows: *apoE3* > *apoE2*(Arg158-->Cys) > *apoE*(Arg145-->Cys) > *apoE* (Arg142-->Cys) approximately *apoE* -Leiden (the latter two usually displaying very little, if any, enhanced binding and uptake). Thus, a correlation exists between the mode of expression of type III hyperlipoproteinemia and the binding and uptake of the specific *apoE* mutation.

; Apolipoproteins E--genetics--GE; *Cholesterol* Esters--biosynthesis--BI ; Fibroblasts--metabolism--ME; Heparan Sulfate Proteoglycan; Heparin Lyase; Hyperlipoproteinemia--metabolism--ME; Ligands; Lipoproteins, VLDL --metabolism--ME; Liver--metabolism--ME; Polysaccharide-Lyases--metabolism ...

Chemical Name: Apolipoproteins E; *Cholesterol* Esters; Heparan Sulfate Proteoglycan; Ligands; Lipoproteins, VLDL; Proteoglycans; Receptors, LDL; Heparitin Sulfate; Polysaccharide-Lyases; Heparin Lyase

7/3,K/19 (Item 19 from file: 155)

08101422 94167182 PMID: 8121744

The influence of apolipoprotein E polymorphism on plasma concentrations of apolipoprotein B and A-I during the first year of life.

Herrmann W; Hanf S; Kaffarnik H; Motzny S; Reissner J; Steinmetz A
Institut fur Klinische Chemie, Universitat Regensburg, Germany.

Pediatrics (UNITED STATES) Feb 1994, 93 (2) p296-302, ISSN 0031-4005 Journal Code: 0376422
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein (apo)E polymorphism has been shown to be associated with different serum levels of *cholesterol*, apoB, and *apoE*. In clarifying the degree of influence of the *apoE* isoforms, investigations in an early stage of life are useful. The aim of the study was to investigate the

plasma levels of apoB apoA-I as structural proteins low and high density lipoproteins, in relation to *apoE* phenotypes during the first year of life. Conclusions about the relationship between *apoE* phenotype and the development of the lipoprotein patterns can be drawn. The concentrations of apoB and apoA-I in capillary plasma as well as the *apoE* phenotype were estimated in 199 newborns (7 days old) and in follow-up investigations of a subgroup of 45 at 1, 4, 12, 24, and 52 weeks. The phenotype frequencies were as follows: 70% *apoE* *3*/3, 16% *apoE* *3*/4, 10% *apoE* 2/3, 2.5% *apoE* 2/2, and 1.5% *apoE* 4/2. The plasma concentrations of apoB and apoA-I in the newborns (7 days old) averaged 55% of the adult value and increased toward...

... of the first year of life up to approximately 85%. The course of the plasma concentrations of apoB and apoA-I in relation to the *apoE* phenotype showed that, beginning at 24 weeks, the apoB levels were significantly lower for the phenotype E 2/2 and in tendency also for the phenotype E 2/3 in comparison with E 3/3. At the end of the first year of life, the apoB levels in infants with *apoE* phenotype 2/2 increased only by 50% and yielded 0.59 g/L. (ABSTRACT *TRUNCATED* AT 250 WORDS)

7/3,K/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07797409 93252943 PMID: 7683682

Transgenic mice carrying the apolipoprotein E3-Leiden gene exhibit hyperlipoproteinemia.

van den Maagdenberg A M; Hofker M H; Krimpenfort P J; de Bruijn I; van Vlijmen B; van der Boom H; Havekes L M; Frants R R
MGC-Department of Human Genetics, Leiden University, The Netherlands.

Journal of biological chemistry (UNITED STATES) May 15 1993, 268 (14) p10540-5, ISSN 0021-9258 Journal Code: 2985121R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... apo) E3-Leiden, described in a large Dutch family, is associated with a dominantly inherited form of familial dysbetalipoproteinemia. To study the effect of the *APOE***3*-Leiden mutation in vivo, transgenic mice were generated using a genomic 27-kilobase DNA construct isolated from the *APOE***3*-Leiden proband. This construct carried the *APOE* gene, the APOC1 gene, and all known regulatory elements including an element that mediates liver expression. Three strains were generated that showed human *APOE* and APOC1 expression. All strains had significantly elevated levels of total plasma *cholesterol* and triglycerides on a regular diet. When mice of one strain were fed a semisynthetic *cholesterol*-rich diet, total plasma *cholesterol* and triglyceride levels increased dramatically. This increase was observed mainly in the very low density lipoprotein (VLDL)- and low density lipoprotein (LDL)-sized fractions. In *cholesterol*-fed mice, the *apoE3* -Leiden protein became equally distributed between the VLDL/LDL and HDL-sized fractions, while in mice kept on a regular diet, *apoE3* -Leiden protein was mainly associated with HDL-sized fractions. The presence of hyperlipoproteinemia in the *APOE***3* -Leiden-expressing transgenic mice supports our finding that the *apoE3*-Leiden *variant* behaves like a dominant trait in the expression of familial dysbetalipoproteinemia. *ApoE3*-Leiden transgenic mice may serve as a model to elucidate additional factors involved in the metabolism of *apoE* containing remnant lipoproteins in general and the etiology of familial dysbetalipoproteinemia in particular.

; Apolipoproteins C--genetics--GE; Apolipoproteins C--metabolism--ME; Apolipoproteins E--blood--BL; Apolipoproteins E--metabolism--ME; Blotting, Northern; *Cholesterol*--blood--BL; *Cholesterol*, Dietary; Cosmids; DNA --genetics--GE; Gene Library; Hyperlipoproteinemia--blood--BL; Hyperlipoproteinemia--metabolism--ME; Kidney--metabolism--ME; Liver --metabolism--ME; Mice; Mice, Inbred C57BL; Mice, Inbred...

Chemical Name: Apolip oteins C; Apolipoproteins E; *Cholesterol*, Dietary; Cosmids; Triglycerides; apolipoprotein C-I; apolipoprotein E-3; *Cholesterol*; RNA; DNA

7/3,K/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07563609 93018536 PMID: 1402403

***Cholesterol* absorption and synthesis related to low density lipoprotein metabolism during varying *cholesterol* intake in men with different apoE phenotypes.**

Gylling H; Miettinen T A
Second Department of Medicine, University of Helsinki, Finland.

Journal of lipid research (UNITED STATES) Sep 1992, 33 (9) p1361-71, ISSN 0022-2275 Journal Code: 0376606
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

***Cholesterol* absorption and synthesis related to low density lipoprotein metabolism during varying *cholesterol* intake in men with different apoE phenotypes.**

The aim of the present study was, first, to investigate whether *cholesterol* (C) absorption, enhanced by *cholesterol* feeding, was related to synthesis of *cholesterol* , serum level of low density lipoprotein (LDL)-C, and receptor activity for LDL apolipoprotein (apo) B in healthy men. Secondly, we were interested in whether *apolipoprotein* *E* (*apoE*) phenotypes contributed to *cholesterol* and LDL apoB metabolism under these conditions. We studied 29 home-living men aged 55 +/- 1 (mean +/- SE) years on a low-fat, low *cholesterol* (208 +/- 13 mg/day) diet followed by a low-fat high *cholesterol* (878 +/- 38 mg/day) diet during 5 weeks. *Cholesterol* feeding increased total *cholesterol*, LDL-C, high density lipoprotein (HDL)-C, and LDL apoB levels from 10% to 13% (P less than 0.05) and bile acid production and *cholesterol* turnover by 16% (P less than 0.05), decreased the fractional catabolic rate (FCR) for LDL apoB by 10% (P less than 0.05) and *cholesterol* absorption efficiency by 8% (P less than 0.05), while *cholesterol* synthesis only tended to decrease. During the *cholesterol* feeding, LDL-C was positively related to apoB production rate and *cholesterol* absorption efficiency (P less than 0.05), and negatively related to bile acid and *cholesterol* synthesis (P less than 0.05) and FCR for LDL apoB, which, in turn, was negatively related to *cholesterol* absorption efficiency and positively to bile acid synthesis. *ApoE* phenotype was positively related to TC, LDL-C, and LDL apoB levels and negatively to FCR for LDL apoB. The increase of the LDL-C level by the high *cholesterol* intake was positively correlated with LDL-C on high *cholesterol* diet and *apoE* phenotypes, so that the increase was 7% in *apoE2* (ns), 11% in *apoE3* (P less than 0.05), and 18% in *apoE4* (P less than 0.05); the increase of bile acid synthesis was significant only in subjects with *apoE2*. Moreover, the increase of LDL-C was positively related to the absolute amount of dietary *cholesterol* absorbed and negatively to FCR for LDL apoB. The findings suggest that the higher the LDL-C level, the higher is the absorption efficiency of *cholesterol* and production of LDL apoB, and the lower is the removal of LDL apoB and synthesis of both bile acids and *cholesterol*, and the more frequently the subjects had epsilon 4 allele. The nonresponsiveness to dietary *cholesterol* was dependent on low LDL-C level, *apoE2* phenotype, and effective bile acid synthesis.(ABSTRACT *TRUNCATED* AT 400 WORDS)

Descriptors: Apolipoproteins E--blood--BL; **Cholesterol*--metabolism--ME ; **Cholesterol*, Dietary--administration and dosage--AD; *Lipoproteins, LDL--blood--BL; *Phenotype; Absorption; Apolipoproteins B--blood--BL; Bile Acids and Salts--metabolism--ME; *Cholesterol*--biosynthesis--BI; Dietary Fats--administration and dosage--AD; Feces--chemistry--CH; Kinetics; Lipoproteins, HDL *Cholesterol*--blood--BL; Lipoproteins, LDL *Cholesterol* --blood--BL; Middle Age; Sterols--metabolism--ME

Chemical Name: Apolipoproteins B; Apolipoproteins E; Bile Acids and Salts ; *Cholesterol*, Dietary; Dietary Fats; Lipoproteins, HDL *Cholesterol*; Lipoproteins, LDL; Lipoproteins, LDL *Cholesterol*; Sterols; *Cholesterol*

7/3,K/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07538997 92407459 PMID: 1388198
Modulation of plasma triglyceride levels by apoE phenotype: a meta-analysis.
Dallongeville J; Lussier-Cacan S; Davignon J
Hyperlipidemia and Atherosclerosis Research Group, Clinical Research Institute of Montreal, Quebec, Canada.
Journal of lipid research (UNITED STATES) Apr 1992, 33 (4) p447-54, ISSN 0022-2275 Journal Code: 0376606
Document type: Journal Article; Meta-Analysis
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The relationship between *apoE* phenotype and plasma lipid levels was analyzed in the combined data of published studies. Accordingly, 45 population samples from 17 different countries were included in the analysis. The mean plasma values of *cholesterol* (CH), triglyceride (TG), and high density lipoprotein (HDL)-CH of the *apoE* 2/2, 3/2, 4/3, 4/4, and 4/2 groups were compared with the same parameters of the E 3/3 subset. The standardized difference between the plasma lipid concentrations of the *apoE* subgroups and of their respective *apoE* *3*/3 control (Z-score), as well as their mean weighted value, were calculated for each study and in each subgroup. The analysis confirmed that subjects...

... epsilon 4 alleles had, respectively, lower (Z2/2 = -0.39, Z3/2 = -0.34) and higher (Z4/3 = 0.15, Z4/4 = 0.29) plasma *cholesterol* values than subjects carrying the epsilon 3/epsilon 3 genotype. In addition, results indicated a consistent relationship between plasma TG levels and *apoE* phenotype among different populations. TG concentrations were significantly higher in *apoE* 2/2, 3/2, 4/3 and E 4/2 than in E 3/3 subsets (Z2/2 = 0.42, Z3/2 = 0.14, Z4...

... and children, in diabetic and obese individuals, as well as in hyperlipidemic subjects indicating an ubiquitous relationship. Concurrently, HDL-CH was significantly lower in the *apoE* 4/3 (Z4/3 = -0.09) than in the E 3/3 subset. (ABSTRACT *TRUNCATED* AT 250 WORDS)
; Adolescent; Adult; Aged; Apolipoproteins E--blood--BL; Child; Child, Preschool; Lipoproteins, HDL *Cholesterol*--blood--BL; Meta-Analysis; Middle Age; Phenotype
Chemical Name: Apolipoproteins E; Lipoproteins, HDL *Cholesterol*; Triglycerides

7/3,K/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07083470 91324501 PMID: 1864973
Familial dysbetalipoproteinemia associated with apolipoprotein E3-Leiden in an extended multigeneration pedigree.
de Knijff P; van den Maagdenberg A M; Stalenhoef A F; Leuven J A; Demacker P N; Kuyt L P; Frants R R; Havekes L M
Institute of Ageing and Vascular Research, Netherlands Organization for Applied Scientific Research, Leiden.
Journal of clinical investigation (UNITED STATES) Aug 1991, 88 (2) p643-55, ISSN 0021-9738 Journal Code: 7802877
Document type: Journal Article
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed

By the careful screening of familial dysbetalipoproteinemic (FD) patients, five probands showing heterozygosity for the *APOE***3*-Leiden allele were found. Genealogical studies revealed that these probands share common ancestry in the 17th century. In a group of 128 family members, spanning three generations, 37 additional heterozygous *APOE***3*-Leiden gene carriers were detected. Although with a variable degree of severity, all carriers exhibited characteristics of FD such as (a) elevated levels of *cholesterol* in the very low density lipoprotein (VLDL) and intermediate density lipoprotein (IDL) fractions, (b) elevated ratios of *cholesterol* levels in these density fractions over total plasma levels of triglycerides, and (c) strongly increased plasma levels of *apolipoprotein* *E* (*apoE*). Multiple linear regression analysis revealed that most of the variability in expression of FD in *APOE***3*-Leiden allele carriers can be explained by age. Body mass index showed a less significant influence on the expression of FD. Gender had no effect on the expression in E*3-Leiden allele carriers, nor did it influence the age of onset of FD. In the group of *APOE***3*-Leiden allele carriers, we found that the E*2 allele enhances the expression of FD, whereas the E*4 allele had the opposite effect. Isoelectric focusing of plasma and of isolated VLDL, IDL, and high density lipoprotein density fractions showed that in E*3-Leiden allele carriers the *apoE3*-Leiden *variant* largely predominates over its normal *apoE* counterpart, especially in the VLDL and IDL density fractions. We conclude that in *APOE***3*-Leiden allele carriers FD is dominantly inherited with a high rate of penetrance, i.e., the presence of normally functioning *apoE* molecules in the plasma does not prevent the age-related expression of this disease.

; Adolescent; Adult; Age Factors; Aged; Alleles; Body Weight; *Cholesterol*--analysis--AN; Heterozygote; Heterozygote Detection; Lipoproteins--analysis--AN; Lipoproteins, VLDL *Cholesterol*--analysis--AN; Middle Age; Pedigree; Sex Factors

Chemical Name: Apolipoproteins E; Lipoproteins; Lipoproteins, VLDL *Cholesterol*; apolipoprotein E-3 Leiden; lipoprotein *cholesterol*; *Cholesterol*

7/3,K/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07070348 91311264 PMID: 1713245

Characterization of a new apolipoprotein E5 variant detected in two French-Canadian subjects.

Mailly F; Xu C F; Xhignesse M; Lussier-Cacan S; Talmud P J; Davignon J; Humphries S E; Nestruck A C

Arterial Disease Research Group, Sunley Research Centre, Hammersmith, United Kingdom.

Journal of lipid research (UNITED STATES) Apr 1991, 32 (4) p613-20, ISSN 0022-2275 Journal Code: 0376606

Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

We have found a novel *apoE5* mutation, using isoelectric focusing (IEF), in two apparently unrelated French-Canadian subjects. Co-dominant inheritance was demonstrated in the family of the first proband, a healthy male subject. The presence of the *apoE5* form was not associated with lipid abnormalities or cardiovascular disease in this family. The second proband was a hyperlipidemic female patient suffering from angina, with... ... the loss of two overlapping epitopes at the amino terminus of the protein. Cysteamine treatment of the very low density lipoproteins indicated that the mutant *apoE* contained only one cysteine residue, suggesting that *apoE3* was the parental form. Two-dimensional electrophoresis suggested that the mutated protein had a slightly lower

molecular weight (by 1-2 kb). However, DNA sequencing of the third exon of the *apoE* gene in both probands revealed a single G to A substitution at the 48th nucleotide, changing the amino acid at position 13 from glutamic acid to lysine. These results were confirmed by oligo melting experiments with allele-specific probes in relatives of the probands. The study of this *apoE* *variant* should provide additional insight into the structure-function relationship of *apoE*.

; Adult; Alleles; Amino Acid Sequence; Apolipoproteins E--immunology--IM; Base Sequence; Epitopes; *Hyperlipidemia*, Familial Combined--genetics--GE; Lipoproteins, VLDL--genetics--GE; Middle Age; Molecular Sequence Data; Mutation; Pedigree

7/3,K/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07053841 91294720 PMID: 1648586

Two apolipoprotein E5 variants illustrate the importance of the position of additional positive charge on receptor-binding activity.

Wardell M R; Rall S C; Schaefer E J; Kane J P; Weisgraber K H
Gladstone Foundation Laboratories for Cardiovascular Disease, Department of Pathology, University of California, San Francisco 94140-0608.

Journal of lipid research (UNITED STATES) Mar 1991, 32 (3) p521-8, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL41633; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Apolipoprotein (apo) E polymorphism has a significant effect on plasma *cholesterol* and low density lipoprotein *cholesterol* concentrations. The association of two *apoE5* isoforms with elevated plasma low density lipoprotein *cholesterol* levels in two unrelated subjects led us to investigate the primary structures and receptor-binding properties of their *apoE* . Cysteamine modification and isoelectric focusing demonstrated that the *apoE5* isoform from subject 1 did not contain cysteine but that the *apoE5* isoform from subject 2 contained one residue of cysteine. The structural mutation in the *apoE5* isoform of subject 1 was determined by peptide sequencing. Like *apoE4*, this *variant* had arginine at position 112 but differed from *apoE4* by the substitution of arginine for proline at position 84. When purified and subjected to a competitive binding assay, this *apoE5*(84 Pro----Arg, 112 Cys----Arg) *variant* had the same receptor-binding activity as normal *apoE3* . Because subject 2 was of Japanese descent and her *apoE5* contained one cysteine residue, we suspected that it would contain the lysine-forglutamic acid mutation at position 3 that has been described previously in Japanese subjects. This was confirmed by directly sequencing the first 10 amino acid residues of her *apoE*. When subjected to the competitive binding assay, the total *apoE* from subject 2, which consisted of approximately equal amounts of normal *apoE3* and *apoE5*(3 Glu----Lys), had a binding activity of 188%, confirming the previously reported enhanced binding of this *variant*. These results demonstrate that the enhancement of receptor-binding activity of more basic isoforms of *apoE* depends on the position at which additional positively charged amino acids are incorporated.

7/3,K/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06883792 91123902 PMID: 2280190

Apolipoprotein E distribution among human plasma lipoproteins: role of the cysteine-arginine interchange at residue 112.

Weisgraber K H
Gladstone Foundation Laboratories for Cardiovascular Disease, Department

of Pathology, University of California, San Francisco 94140-0608.
Journal of lipid research (UNITED STATES) Aug 1990, 31 (8) p1503-11, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL41633; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Human apolipoprotein (apo) E occurs as three common isoforms (*apoE4*, E3, and E2), all of which influence plasma *cholesterol* levels. Although both *apoE4* and E3 bind with equal effectiveness to the low density lipoprotein receptor, they associate preferentially with different classes of plasma lipoproteins: *apoE4* with very low density lipoproteins, *apoE3* with high density lipoproteins. The primary structure of *apoE3* differs from that of *apoE4* at only a single site; *apoE3* has its sole cysteine residue at position 112, while *apoE4* contains arginine at position 112 and completely lacks cysteine. The present study investigated how this structural difference between *apoE4* and E3 determines their distribution among plasma lipoproteins, and analyzed the role of the disulfide-linked heterodimer *apoE*-A-II (which *apoE4* cannot form) in determining the distribution. Human plasma was incubated with 125I-labeled *apoE*, and lipoproteins were separated by agarose chromatography. Both *apoE3* that had been reduced and alkylated with iodoacetamide and *apoE3* -A-II distributed with high density lipoproteins, indicating that a combination of an inherent property of the monomeric *apoE3* structure and *apoE*-A-II formation account for distribution of *apoE3* to the high density lipoproteins. Cysteamine modification of *apoE3* resulted in an *apoE4* -like distribution, demonstrating that a positive charge at position 112 determined the *apoE4* distribution and that the effect was not exclusively due to the presence of arginine at this position. (ABSTRACT *TRUNCATED* AT 250 WORDS)

7/3,K/27 (Item 27 from file: 155)

06631946 90257516 PMID: 2341812
Apolipoprotein E2-Dunedin (228 Arg replaced by Cys): an apolipoprotein E2 variant with normal receptor-binding activity.
Wardell M R; Rall S C; Brennan S O; Nye E R; George P M; Janus E D; Weisgraber K H
Department of Pathology, University of California, San Francisco 94140-0608.
Journal of lipid research (UNITED STATES) Mar 1990, 31 (3) p535-43, ISSN 0022-2275 Journal Code: 0376606
Contract/Grant No.: HL41633; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Homozygosity for the apolipoprotein (apo) E *variant* *apoE2* (158 Arg----Cys) invariably gives rise to dysbetalipoproteinemia, and when associated with obesity or a gene for *hyperlipidemia*, results in type III hyperlipoproteinemia. The association of the E2/2 phenotype with type IV/V hyperlipoproteinemia rather than type III hyperlipoproteinemia in identical twin brothers led us to investigate the primary structure of their *apoE*. Lipoprotein electrophoresis on agarose gels confirmed the presence of increased very low density lipoproteins (VLDL) and chylomicrons but little, if any, beta-VLDL, indicating that these subjects did not have dysbetalipoproteinemia. When the *apoE* from these twins was subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis on a system that can distinguish *apoE2*(158 Arg----Cys) from all other known *apoE* variants, it gave rise to two components. One had the unique mobility of *apoE2* (158 Arg----Cys), and one migrated in the position of the other

variants of *apoE* (and normal *apoE3*), indicating that t brothers were heterozygous for *apoE2*(158 Arg----Cys) and a second *apoE2* isoform. Cysteamine modification and isoelectric focusing showed that, like *apoE2* (158 Arg----Cys), the second *apoE2* isoform also contained two cysteine residues. The structural mutation in the second *apoE2* isoform was determined by peptide sequencing. Like normal *apoE3*, this *variant* had arginine at position 158, but differed from *apoE3* by the substitution of cysteine for arginine at position 228. Total *apoE* isolated from the brothers had the same receptor-binding activity in a competitive binding assay as a 1:1 mixture of normal *apoE3* and *apoE2* (158 Arg----Cys).(ABSTRACT *TRUNCATED* AT 250 WORDS)

7/3,K/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06548652 90173805 PMID: 2308518
A high carbohydrate-fat free diet alters the proportion of heparin-bound VLDL in plasma and the expression of VLDL-apoB-100 epitopes.
Keidar S; Goldberg A C; Cook K; Bateman J; Schonfeld G
Department of Medicine, Washington University School of Medicine, St Louis, MO.
Metabolism- clinical and experimental (UNITED STATES) Mar 1990, 39 (3) p281-8, ISSN 0026-0495 Journal Code: 0375267
Contract/Grant No.: HL15308; HL; NHLBI; HL32000; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

... epitopes of apoB-100. The CHO diet produced consistent increases of plasma triglycerides in all subjects by a mean of 66% and decreases in plasma *cholesterol* by 18%. ApoB in plasma decreased by 21% and apoA-I by 17%; however, *apoE* and ApoA-II did not change. VLDL was enriched with triglycerides (55.0% +/- 0.8 v 57.0% +/- 0.7, P less than .05) and *apoE* (*3*.7% +/- 0.5 to 5.9% +/- 0.7, P less than .007) and the ratio between *apoE* and apoC in VLDL increased (0.15 +/- 0.03 to 0.25 +/- 0.03, P less than .002).(ABSTRACT *TRUNCATED* AT 250 WORDS)
...; purification--IP; Binding Sites--drug effects--DE; Chromatography, Affinity; Cross Reactions; Electrophoresis, Polyacrylamide Gel; Heparin --metabolism--ME; Lipoproteins, VLDL--isolation and purification--IP; Lipoproteins, VLDL *Cholesterol*--analysis--AN; Phospholipids--analysis--AN ; Radioimmunoassay
Chemical Name: Antibodies, Monoclonal; Apolipoproteins B; Apolipoproteins C; Apolipoproteins E; Dietary Carbohydrates; Dietary Fats; Lipoproteins, VLDL; Lipoproteins, VLDL *Cholesterol*; Phospholipids; apolipoprotein B-100 ; Heparin

7/3,K/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05353039 87031249 PMID: 3770314
Apolipoprotein E polymorphism and hyperlipemia in type II diabetics.
Eto M; Watanabe K; Iwashima Y; Morikawa A; Oshima E; Sekiguchi M; Ishii K
Diabetes (UNITED STATES) Dec 1986, 35 (12) p1374-82, ISSN 0012-1797 Journal Code: 0372763
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The relationship between *apolipoprotein* *E* (*apoE*) polymorphism and plasma lipids and hyperlipemia was investigated in 105 male type II diabetics and 111 male nondiabetics. *ApoE* phenotypes were determined by a

one-dimensional rapid fl[redacted] gel isoelectric focusing met as described previously. The *apoE* phenotype frequency in diabetics was similar to that in nondiabetics. The frequency of hyperlipemia was higher in diabetics (56.2%) than in nondiabetics (32.4%). It was highest in the *apoE3*/2 group of diabetics and nondiabetics, followed by the *apoE4*/3 and *apoE3*/3 groups in the order described, indicating that the susceptibility to hyperlipemia differs among the *apoE* phenotype groups. *ApoE3*/2 diabetics had significantly higher levels of *apoE* and very-low-density lipoprotein (VLDL) *cholesterol* (chol)/VLDL triglyceride (TG) ratios than *apoE3*/3 diabetics. The effects of diabetes mellitus on plasma lipid levels differed among the various *apoE* phenotype groups: i.e., plasma total chol and low-density lipoprotein (LDL) chol increased only in *apoE3*/2 and *apoE4* /3 diabetics and plasma high-density lipoprotein chol decreased only in *apoE3*/3 diabetics, as compared with the corresponding *apoE* phenotype groups of nondiabetics, whereas plasma TG, VLDL TG, and VLDL chol increased in the three *apoE* phenotype diabetics. Furthermore, an increase of *apoEII*:*apoEIII* ratio was observed in *apoE3*/3 diabetics, particularly in those with hypertriglyceridemia. This study has also shown that the increased *apoEII*:*apoEIII* ratio is due to increased sialation of *apoE* based on the study of sialidase digestion of apo VLDL.(ABSTRACT *TRUNCATED* AT 250 WORDS)

Descriptors: Apolipoproteins E--genetics--GE; *Diabetes Mellitus, Non-Insulin-Dependent--complications--CO; **Hyperlipidemia*--complications --CO; Adult; Apolipoproteins E--isolation and purification--IP; Diabetes Mellitus, Non-Insulin-Dependent--genetics--GE; *Hyperlipidemia*--genetics --GE; Isoelectric Focusing; Lipids--blood--BL; Lipoproteins--blood--BL; Lipoproteins, VLDL--blood--BL; Middle Age; Phenotype; Polymorphism (Genetics)

7/3,K/30 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09686679 BIOSIS NO.: 199598141597
Identification and characterization of a novel *apolipoprotein* *E* *variant*, apolipoprotein E3' (Arg-136 fwdarw His): Association with mild dyslipidemia and double pre-beta very low density lipoproteins.
AUTHOR: Minnich Anne(a); Weisgraber Karl H; Newhouse Yvonne; Dong Li-Ming; Fortin Louis-Jacques; Tremblay Michel; Davignon Jean
AUTHOR ADDRESS: (a)Clinical Res. Inst. Montreal, 110 Pine Ave. West, Montreal, PQ H2W 1R7**Canada
JOURNAL: Journal of Lipid Research 36 (1):p57-66 1995
ISSN: 0022-2275
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

Identification and characterization of a novel *apolipoprotein* *E* *variant*, apolipoprotein E3' (Arg-136 fwdarw His): Association with mild dyslipidemia and double pre-beta very low density lipoproteins.

ABSTRACT: Apolipoprotein (apo) E mediates the removal of chylomicron and VLDL remnants from plasma. In a proband with mild *hyperlipidemia* and a family history of premature coronary artery disease, we have identified a new mutant of *apoE* with an isoelectric point close to but distinct from that of *apoE3*. Sequencing of the *apoE* gene from this subject (JB) revealed that the subject was heterozygous for a G to A substitution in codon 136, resulting in the substitution of histidine for arginine; therefore, we have designated this isoform *apoE3*' (Arg-136 fwdarw His). Examination of the proband's kindred revealed that the nine carriers (all heterozygotes) of the *variant* isoform displayed a twofold elevation in the concentration of very low density lipoprotein (VLDL) *cholesterol* (40 +- 8 mg/dl) and triglyceride (109 +- 19) compared to the nine noncarriers (19 +- 3 and 55 +- 13, respectively). In all carriers, the VLDL displayed an abnormal double pre-beta pattern upon electrophoresis. The low density lipoprotein receptor-binding activity of purified *apoE3*

'(Arg-136 fwdarw His) wh[redacted] complexed with DMPC was slight[redacted] defective (80% of the activity of normal *apoE*). The mutant *apoE* also displayed a reduced affinity for heparin compared to *apoE3*. As both of these biochemical parameters are known to be important in VLDL clearance, the defects associated with this *variant* are likely responsible for the increase in VLDL observed in carriers. None of the carriers displayed clinical features of type III hyperlipoproteinemia, suggesting that the relatively mild dyslipoproteinemic phenotype associated with this *variant* might be associated with recessive expression of this disorder. However, the abnormal VLDL phenotype appears to be dominantly expressed.

7/3,K/31 (Item 2 from file: 5)

09584973 BIOSIS NO.: 199598039891

Plasma lipoproteins in familial dysbetalipoproteinemia associated with apolipoproteins E2(Arg158 fwdarw Cys), E3-Leiden, and E2 (Lys146 fwdarw Gln), and effects of treatment with simvastatin.

AUTHOR: Zhao Shui-Ping; Smelt Augustinus H M; Van Den Maagdenberg Arn M J M ; Van Tol Arie; Vroom Ton F F P; Leuven Jan A Gevers; Frants Rune R; Havekes Louis M; Van Der Laarse Arnoud(a); Van't Hoft Ferdinand M
AUTHOR ADDRESS: (a)Dep. Cardiol. Build. 1 C5-P24, Univ. Hosp., Rijnsburgerweg 10, 2333 AA Leiden**Netherlands

JOURNAL: Arteriosclerosis and Thrombosis 14 (11):p1705-1716 1994
ISSN: 1049-8834
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

...ABSTRACT: in detail the plasma lipoprotein profiles of 18 patients with familial dysbetalipoproteinemia (FD) who had apolipoprotein (apo) E2(Arg158 fwdarw Cys) homozygosity (the E2-158 *variant*, n=6), *apoE3* -Leiden heterozygosity (the E3-Leiden *variant*, n=6), or *apoE2*(Lys146 fwdarw Gln) heterozygosity (the E2-146 *variant*, n=6), with average plasma *cholesterol* concentrations of 8.99+-1.34 mmol/L, 9.29 +- 1.55 mmol/L, and 8.46 +- 1.10 mmol/L, respectively. No significant differences ...

...and intermediate-density lipoprotein (IDL) and a higher cholesteryl ester content of VLDL1 and VLDL2 than in 6 normolipidemic control subjects with an average plasma *cholesterol* concentration of 5.90+-0.53 mmol/L. Major differences between the plasma lipoprotein profiles of patients with the E2-158 *variant*, the E3-Leiden *variant*, and the E2-146 *variant* and the normolipidemic control subjects were in IDL *cholesterol* concentration (1.70+-0.26, 1.50+-0.26, 1.05+-0.36, and 0.47+-0.14 mmol/L, respectively), LDL *cholesterol* concentration (1.83+-0.50, 3.09+-0.32, 3.79+-0.76, and 3.77+-0.56 mmol/L, respectively), and the molar ratio of IDL *cholesterol* to LDL *cholesterol* (0.98+-0.28, 0.48+-0.04, 0.28+-0.09, and 0.12+-0.03, respectively). After 10 weeks of simvastatin treatment the concentrations of plasma *cholesterol*, VLDL2 *cholesterol*, IDL *cholesterol*, and LDL *cholesterol* in 3 patients with the E2-158 *variant* fell significantly, by 46%, 56%, 53%, and 48%, respectively; they also fell in 3 patients with the E3-Leiden *variant*, by 48%, 54%, 57%, and 52%, respectively, and in 3 patients with the E2-146 *variant*, by 38%, 55%, 46%, and 35%, respectively. Simvastatin therapy lowered plasma activity of cholesteryl ester transfer protein but had no significant effect on plasma activity of lecithin: *cholesterol* acyltransferase. It is concluded that patients with FD due to various *apoE* variants have different lipoprotein profiles, mainly with regard to IDL and LDL levels, although they have a number of similar features of dysbetalipoproteinemia. Simvastatin therapy Effectively reduced the plasma concentrations of total *cholesterol*, VLDL2 *cholesterol*, IDL *cholesterol*, and LDL *cholesterol* in the three groups of patients studied. It is proposed that *apoE*-dependent defects of the conversion of IDL to LDL may be an important mechanism in

the pathophysiology of F
...REGISTRY NUMBERS: *CHOLESTEROL*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: ...*CHOLESTEROL*
MISCELLANEOUS TERMS: *CHOLESTEROL*;

7/3,K/32 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08749364 BIOSIS NO.: 199395038715
Familial apolipoprotein E deficiency and type III hyperlipoproteinemia due to a premature stop codon in the apolipoprotein E gene.
AUTHOR: Lohse Peter; Breweri H Bryan Ii; Meng Martha S; Skarlatos Sonia I; Larosa John C; Brewer H Bryan Jr
AUTHOR ADDRESS: Build. 10, Room 7N117, Natl. Inst. Health, 9000 Rockville Pike, Bethesda, Md. 20892**
JOURNAL: Journal of Lipid Research 33 (11):p1583-1590 1992
ISSN: 0022-2275
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A kindred with *apolipoprotein* *E* deficiency and a *truncated* lower molecular weight *apoE* mutant, designated *apoE*-*3*-Washington, has been identified. Gel electrophoresis demonstrated complete absence of the normal *apoE* isoproteins and the presence of a small quantity of a lower molecular weight *apoE*. Plasma *apoE* levels in the proband were approximately 4% of normal. This marked deficiency of *apoE* resulted in delayed uptake of chylomicron and very low density lipoprotein (VLDL) remnants by the liver, elevated plasma *cholesterol* levels, mild hypertriglyceridemia, and the development of type III hyperlipoproteinemia. Sequence analysis of the patient's *apoE* gene revealed a single nucleotide substitution of an A for a G, which converted amino acid 210 of the mature protein, tryptophan (TGG), to a premature chain termination codon (TAG), thus leading to the synthesis of a *truncated* E apolipoprotein of 209 amino acids with a molecular mass of 23.88 kDa. Northern blot analysis of differentiated monocyte-derived macrophages demonstrated a mutant mRNA indistinguishable in size from normal *apoE* mRNA. The nucleotide substitution also resulted in the formation of a new restriction site for Mae I. Using this enzyme we were able to establish...

...proband is a homozygote and that her two offsprings are heterozygous for the epsilon-3-Washington allele. These data demosntrate that the striking deficiency of *apoE*-*3*-Washington results in a moderate form of type III hyperlipoproteinemia. The clinical presentation also suggests a dispensable role of *apoE* in the nervous system and in immunoregulation.
...REGISTRY NUMBERS: *CHOLESTEROL*
DESCRIPTORS:
CHEMICALS & BIOCHEMICALS: *CHOLESTEROL*
MISCELLANEOUS TERMS: *CHOLESTEROL*;

7/3,K/33 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07057820 BIOSIS NO.: 000089127924
APOLIPOPROTEIN E2-DUNEDIN 228 ARG-CYS AN APOLIPOPROTEIN E2 VARIANT WITH NORMAL RECEPTOR-BINDING ACTIVITY
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JOURNAL: J LIPID RES 31 (3). 1990. 535-544. 1990

FULL JOURNAL NAME: Journal Lipid Research
CODEN: JLPRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Homozygosity for the apolipoprotein (apo) E *variant* *apoE2*(158 Arg.fwdarw.Cys) invariably gives rise to dysbetalipoproteinemia, and when associated with obesity or a gene for *hyperlipidemia*, results in type III hyperlipoproteinemia. The association of the E2/2 phenotype with type IV/V hyperlipoproteinemia rather than type III hyperlipoproteinemia in identical twin brothers led us to investigate the primary structure of their *apoE*. Lipoprotein electrophoresis on agarose gels confirmed the presence of increased very low density lipoproteins (VLDL) and chylomicrons but little, if any, .beta.-VLDL, indicating that these subjects did not have dysbetalipoproteinemia. When the *apoE* from these twins was subjected to sodium dodecyl sulfate-polyacrylamide gel electrophoresis on a system that can distinguish *apoE2*(158 Arg.fwdarw.Cys) from all other known *apoE* variants, it gave rise to two components. One had the unique mobility of *apoE2*(158 Arg.fwdarw.Cys), and one migrated in the position of the other variants of *apoE* (and normal *apoE3*), indicating that the brothers were heterozygous for *apoE2*(158 Arg.fwdarw.Cys) and a second isoform. Cysteamine modification and isoelectric focusing showed that, like *apoE2*(158 Arg.fwdarw.Cys), the second *apoE2* isoform also contained two cysteine residues. The structural mutation in the second *apoE2* isoform was determined by peptide sequencing. Like normal *apoE3*, this *variant* had arginine at position 158, but differed from apo3 by the substitution of cysteine for arginine at position 228. Total *apoE* isolated from the brothers had the same receptor-binding activity in a competitive binding assay as a 1;1 mixture of normal *apoE3* and *apoE2*(158 Arg.fwdarw.Cys). Since the brothers possess approximately equal amounts of *apoE2*(158 Arg.fwdarw.Cys) and *apoE2*(228 Arg.fwdarw.Cys), this suggests that *apoE2*(228 Arg.fwdarw.Cys) has normal, or nearly normal, receptor-binding activity. Consequently, with respect to the common polymorphic sites in *apoE* and functional activity, these subjects are indistinguishable from E3/2 individuals, a finding consistent with the apparent absence of .beta.-VLDL and other characteristics of...

7/3,K/34 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

02756751 BIOSIS NO.: 000068067358
TYPE III HYPER LIPO PROTEINEMIA DEVELOPMENT OF A VERY LOW DENSITY LIPO PROTEIN APO LIPO PROTEIN E GEL ISO ELECTRIC FOCUSING TECHNIQUE AND APPLICATION IN FAMILY STUDIES
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JOURNAL: J LAB CLIN MED 93 (4). 1979. 549-569. 1979
FULL JOURNAL NAME: Journal of Laboratory and Clinical Medicine
CODEN: JLCMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

...ABSTRACT: applied to VLDL [very-low-density lipoprotein] isolated from 90 normal and 119 hyperlipoproteinemic subjects including 15 subjects with primary type III hyperlipoproteinemia. Three basic *ApoE* [*apolipoprotein* *E*] isoelectric focusing patterns were observed: a 4-band pattern (*ApoE*-1', 1, 2 and 3) which is the most common; a *variant* pattern containing a 5th *ApoE* subspecies, *ApoE*-4 (28% of all non-type III subjects); and a pattern deficient in both *ApoE*-*3* and *ApoE*-4 subspecies with doubling of the remaining bands, which was unique to the type III subjects. The possibility that a urea decomposition product, cyanate, caused this doubling through *ApoE*

carbamylation was ruled [redacted]. The inclusion of a disulfide [redacted]ducing agent, DTT [dithiothreitol] in the ApoVLDL solubilization medium eliminated the doubling. The effects of albumin and ApoA-I contamination in isolated VLDL were investigated. Albumin is the more serious, since its focusing pattern makes interpretation and quantitation of *ApoE*-*3* and *ApoE*-4 tenuous; but the technique described separates albumin from VLDL. Inclusion of DTT in the ApoVLDL solubilization medium was necessary for the discrimination of the unaffected (normal) from the intermediate (heterozygous) *ApoE* pattern on the basis of *ApoE*-*3*/*ApoE*-2 ratios (R) of the stained bands. This cutoff point was established by the study of 20 obligate heterozygotes. The R was then used to classify subjects as *ApoE*-*3* deficient (R < 0.2), intermediate (0.2 < R < 1.1), or unaffected (R > 1.10). The genetic transmission of the type III disease was studied in 7 kindred, each ascertained through an affected proband. Using gel isoelectric focusing of ApoVLDL *ApoE*, each family member was classified into 1 of the 3 above categories corresponding to the 3 genotypes of a 2-allele autosomal system. Segregation analysis of informative matings was consistent with Utermann's autosomal recessive hypothesis. All subjects with clinical type III disease had an *ApoE*-*3* /Apo-2 ratio indicating the deficient category. Not all deficients had clinical type III disease, suggesting that other factors, either genetic or environmental, are required...

...manifestation of clinical symptoms in the at risk homozygotes. No increase in other types of hyperlipoproteinemia was observed in these families, but several of the *ApoE*-*3*-deficient kindred had low levels of LDL [low density lipoprotein] *cholesterol* consistent with hypobetalipoproteinemia.

DESCRIPTORS: HUMAN *CHOLESTEROL* EXPRESSIVITY PENETRANCE ALBUMIN HYPO BETA LIPO PROTEINEMIA UREA CYANATE DI THIO THREITOL AUTOSOMAL RECESSIVE INHERITANCE

?ds

Set	Items	Description
S1	948	((APOE?) OR (APOE) OR (APOLIPOPROTEIN (W) E)) (S) (TRUNCATED OR VARIANT OR DELETED)
S2	326	S1 AND (HYPERLIPIDEMIA OR CHOLESTEROL)
S3	23	S2 AND (VECTOR OR ADENOVIRUS)
S4	11	RD (unique items)
S5	79	S2 AND ((APOE3) OR (APOE (W) 3))
S6	41	RD (unique items)
S7	34	S6 NOT S4

?logoff

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       28jul03 13:47:47 User259876 Session D527.2
            $3.97    1.240 DialUnits File155
               $7.35  35 Type(s) in Format  3
            $7.35  35 Types
    $11.32  Estimated cost File155
            $3.74    0.668 DialUnits File5
              $17.50  10 Type(s) in Format  3
           $17.50  10 Types
    $21.24  Estimated cost File5
            $1.87    0.334 DialUnits File55
     $1.87  Estimated cost File55
            OneSearch, 3 files,  2.242 DialUnits FileOS
     $1.62  TELNET
    $36.05  Estimated cost this search
    $36.40  Estimated total session cost   2.332 DialUnits
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Status: Signed Off. (7 minutes)